Final report of research

Evaluation of the therapeutic and prophylactic effects of Tinapeg® versus Neulastim® on the absolute neutrophil counts after chemotherapy in patients with breast cancer

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Addres: AryaTinaGene Biopharmaceuticals Co. Second Sazandegi, Aqqalla Industrial Zone, Gorgan, Iran

Zip Code: 4931171756

Tel:+9817 34533545, +981734533518

Fax:+98 17 34533554

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Study advisory group and their responsibilities:		
Full Name of Specialist	**Expertise**	**Responsibility**
Dr. Seyed Asadollah Mousavi	Hematologh &Oncology	Principal Investigator
Dr. A.H Porkhani	Hematologh &Oncology	Sub-Investigator
Dr. M Naeimi	Hematologh &Oncology	Sub-Investigator
Dr. S.M Razavi	Hematologh &Oncology	Sub-Investigator
Dr. A.R Rezvani	Hematologh &Oncology	Sub-Investigator
Dr. N Ansarinejad	Hematologh &Oncology	Sub-Investigator
Dr. F Fardad	Hematologh &Oncology	Sub-Investigator
Dr. S Tavakoli	Hematologh &Oncology	Sub-Investigator
Dr. M Vaezi	Hematologh &Oncology	Sub-Investigator
Dr. H Kamranzade	Hematologh &Oncology	Sub-Investigator
Dr. N Khodakarim	Hematologh &Oncology	Sub-Investigator
Dr. N Namdari	Hematologh &Oncology	Sub-Investigator

Dr. M.M Adib	Hematologh &Oncology	Sub-Investigator
Dr.V Kaveh	Hematologh &Oncology	Sub-Investigator
Dr. Abbas Keshtkar	Epidemiology and Statistics Expert	Monitoring and Evaluation (RM&E) and Data Management.

Company Representative Profile:

Dr. M.A Afshari	Mycologist	Head of Clinical Trail	Afshari_ma@yahoo.com

Appointed Scientific-Executive Committee:

	Name and Sure name	**Spescialist**	**Tel No.**	**Email**
1	Dr. Majid Shahbazi	Genetic and Immunologist	09125140251	shahbazim@atgbio.com
2	Dr. Shahriyar Omidvar	Pharmacy	09121326209	Sh.omidvar@gmail.com
3	Dr. Hossein Amini	Pharmacologist	09125214855	haminhplc@yahoo.com
4	Dr. Eskandar Omidi niya	Drug Biotechnologist	09123491157	Eomid8@gmail.com
5	Dr. Mohammad Ali Afshari	Mycologist	09123039856	Afshari_ma@yahoo.com
6	Dr. S.Navid Mirghasemi	Veterinary	09126056812	Navid_qasemi2000@gmail.com
7	Dr. Abbas Asadollahi	physician	09307745752	Abbas_asadollahi@yahoo.com
8	Eng. Behnam Taghavi	MBA	09121180952	behnam_durst@yahoo.com
9	Dr. Mohammadmehdi Hadipour	Neuroscientist	09179332824	mm.hadipour@gmail.com

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Study sponsor

The research and production company Arya Tina Gene, a special joint stock company with the registration number 7550 and the National ID 10102706497, was established in 1384 and was launched in 1392, supported the study to released the drug to the market.

Abstract

Since 1940s, chemotherapy was used as a therapeutic strategy for cancer. Unfortunately, along with the beneficial effects of chemotherapy (elimination of cancer cells), natural cells and living tissues, and Different organs of the body, especially cells with fast division, are also subject to varying degrees of damage. Theoretically, all chemotherapy regimens can suppress the immune system and bone marrow. This suppression can lead to the reduction of white blood cells, red blood cells and platelets. The pegfilgrastim is known as an effective and important treatment for prevention of neutrophil counts in the blood. Therefore, the present study was conducted as a clinical trial with the aim of investigating the effectiveness of Pegfiltrastim construct of Arya Tina Gene Company with the Tinapeg brand in chemotherapy-induced neutropenic prophylaxis and treatment and comparison with external specimen. This study was designed as a parallel, randomized, double blind, and multi-center clinical trial. In this way, patients diagnosed with breast cancer who entered the study, were randomly assigned into two groups. 102 eligible patients were enrolled in the study and 51 patients were randomly assigned to the Neulastim drug group. 51 patients were assigned to the tinapeg group. Each patient received a chemotherapy regimen containing doxorubicin 60 mg / m^2 and cyclophosphamide 600 mg / m^2 in day 1 and 24 hours after (the second day) a single 6 mg dose of pegfilgrastim administered subcutaneously. Based on the results, at the begining of the study, the absolute count of neutrophils in the studied groups did not differ significantly. During the four treatment cycles, this parameter progressively increased in both groups. Finally, at the end of the fourth cycle, the mean neutrophil counts in Tinapeg and Neulastim therapy groups increased 26 and 34% respectively, which was not statistically significant. Also, in the fourth cycle, the mean number of neutrophils in the Tinapeg and Neulastim therapy groups was 5315 and 5159. Estimation of the point average of the ratio of the mean values showed that the central index of the absolute number of neutrophils in the tinapeg group was greater than that of neulastim. Other parameters such as platelet count, white blood cell count and hemoglobin levels did not differ significantly between the two groups at the end of the fourth cycle. There was no significant difference between the two groups in terms of incidence of adverse events and unwanted reactions.

فهرست مطالب:

Abbreviations

Definitions:

Subjects: All adult female patients (aged 18 years or older) with breast cancer who require chemotherapy in their healing process and are referred to the Shariati Center of Hematology, Oncology and Stem Cell Transplantation, Rasool Akram, Firoozgar Tehran, Namazi Shiraz and 5 Azar Gorgan.

Equality: The absolute count of the number of neutrophils in a unit cubic milliliter of blood, which was used quantitatively continuously.

Incidence of neutropenic fever: fever over 38.5 ° C for at least an hour and neutropenia less than 500 neutrophils per mm^3

Severe neutropenia: Absolute neutrophil count is less than 500 in 1 µl

Medium neutropenia: Absolute neutrophil count between 500 and 1000 cells in 1 µl

Mild neutropenia: Absolute neutrophil count between 1000 and 1500 cells in 1 µl

Ethical considerations:

Due to the nature of this study and also the need for obtaining biological samples (blood or serum), written consent, which was prepared by the anchors before the beginning of the study, was informed to the patients and they were asked to carefully read the form and sign it after consent. Proposals and protocol of the study were approved at the Tehran University of Medical Sciences and Gorgan University Ethics Committee for Research. The patients were convinced of the confidentiality of their information to the executives of the study.

Data and Safety Monitoring Board (DSMB)

	Name	specialty	Post	Phone No.	E.male
1	Dr. Seyed Asadollah Mousavi	Hematology and Oncology	Principal Investigator	09122387450	A_mosavi@yahoo.com
2	Dr. Mehrzad Mirzaniya	Hematology and Oncology	Independent observer	09122772411	Mirzania_m@yahoo.com
3	Dr. Farhad Shahi	Hematology and Oncology	Independent observer	09121309234	Shahi_f@gmail.com
4	Dr. Abbasali	Statistics and Epidemiology	Statistics Consultant	09127179137	abkeshtkar@gmail.com
5	Dr. Mohammad Ali Afshari	Mycologist	Agent	09123039856	Afshari_ma@yahoo.com

Introduction:

According to World Cancer Report by the Cancer Society in 2012, 14.1 million new cases of cancer have occurred in both sexes, which 8 million cases (82%) are in developing countries (other than non-melanoma skin cancer Whose

statistics are not accurately recorded), and it was the second leading cause of death after cardiovascular events. Respiratory tract cancer (lung, trachea and bronchus) in men and breast cancer in women are ranked first in the world. It was reported that in 2012, 8.2 million cases where dead due to these cancers, which is similar to the incidence of cancer in terms of the prevalence of cancer-causing deaths [1].

From the beginning of the 1940s, chemotherapy was used as a therapeutic strategy for cancer. Since then, much progress has been made in this way, as today chemotherapy, along with radiation therapy and surgery, is one of the common ways to treat malignant cancer patients [2]. Unfortunately, in addition to the beneficial effects of chemotherapy (the elimination of cancer cells), the natural living cells of tissue and organs of the body, especially the cells that have rapid cell division, tolerate various degrees of damage. Different chemotherapy protocols for treatment of various cancers are based on the fundamental principle of maximizing the removal of cancer cells and minimizing the negative effects on healthy and normal cells. Therefore, based on this principle, different chemotherapy protocols are developed for treatment of various cancers, and these protocols are optimized with the advancement of the drugs used in chemotherapy [3].

The complications of various chemotherapy drugs are divided into two groups: common complications and specific side effects of different organs. Common complications include immunosuppression, fatigue, platelet loss, and bleeding tendency, digestive complications (nausea and vomiting), mucosal inflammation and hair loss [2]. Theoretically, all chemotherapy regimens can cause suppression of the immune system and bone marrow, leading to a reduction in white blood cells, red blood cells and platelets.

The frequency of different chemotherapy methods varies in cancer of different organs, and this frequency depends on the type and nature of cancer, the degree of cancer progression, and the general and clinical status of the affected patients. In a study to evaluate the therapeutic pattern of chemotherapy in patient with the breast cancer (65 years of age and older), it has been shown that with the advent of the disease, the use of chemotherapy has increased, so that in stages 1, 2, 3 and 4, the frequency of use of this Methods were 5.1%, 19.5%, 33.9% and 35.2% respectively [4]. In another study from the US Breast Cancer Care Database, about 10,000 women with breast cancer aged 20 years and older were evaluated using a randomized sampling of the database data. The results of

this study showed that the use of chemotherapy (without the use of hormone therapy, such as tamoxifen) in the different groups of these patients varied between about 48% to about 60%. Meanwhile, the frequency of use of different chemotherapy regimens has increased from 1987 to 2000 [5].

The risk of bone marrow suppression and neutropenia is also different in cancer patients. In a survey of about 35,000 women aged 65 and older with breast cancer, according to data from the American Cancer Care System, more than 9% of cancer-causing women received one of the chemotherapy regimens, hospitalized due to fever, neutropenia, thrombocytopenia (Or other systemic complications). However, due to the same complications and disorders in women with cancer without chemotherapy, it was about 0.5%. Additionally, the incidence rate due to these complications at stages 1, 2, 3 and 4 was reported as 6.3, 8.1, 12.3 and 13.2% respectively [6]. In another study on American Cancer Care System data in 15 different geographic areas, about 10,000 women with different stages of ovarian cancer were evaluated for hospitalization due to bone marrow suppression in the period 1991-2002. In this study, 65.7% of the patients were evaluated using a different chemotherapy regimen. Hospitalized risk factors for infections or bone marrow suppression were: chemotherapy regimen containing non-platinum compounds (compared to platinum compounds), comorbidity score, and age [7]. In another comprehensive review, about 65,000 women with breast cancer and about 7,500 women with ovarian cancer aged 65 and older in 16 different regions of the United States (based on cancer care data), the occurrence of chemotherapy-related bone marrow suppression (Regardless of whether it led to hospitalization) was evaluated as the main outcome of the study. Based on the findings of this study, the incidence of short-term neutropenia (within less than 3 months) in different chemotherapy regimens ranged from 11.0 to 47.7 per 1000 person-years for breast cancer and between 25.2 and 80.9 per thousand person-years for Ovarian cancer was different. The incidence of long-term neutropenia (over 3 months) in various chemo-therapeutic regimens in breast cancer varied from 18.8 to 40.6 per 1000 person-years, and for ovarian cancer between 35.3 and 109.1 per 1,000 people in a year. Also, in most chemotherapy regimens, the dose-response relationship between different amounts or chemotherapy cycles was observed with bone marrow toxicity [8]. On the other hand, reducing the dose of chemotherapy or delaying the next cycle [9] in most cancers, including

colorectal cancer [10] lung cancer [11] and breast cancer [12], worsens the patient's prognosis.

Granulocyte colony growth stimulator is a glycoprotein, growth factor or cytokine that is secreted by endothelium cells, macrophages, and some immune cells in the body, and stimulates and distinguishes granulocytes by stimulating bone marrow. Also, this factor is referred to as a strong induction of movement of the stem cells and causes them to enter the peripheral blood.

In addition to the major effects, G-CSF is a neurotrophic factor, with throphic effects on central nervous system, it can induced neurogenesis and prevent neural apoptosis. By relying on this feature, scientists are trying to find new ways to treat diseases of the nervous system [13-15]. For the first time in 1983 the mouse G-CSF was produced in Australia, and its human form was also produced in Japan, America and Germany in 1986 [16-18]. This factor has been used for more than two decades as an undeniable factor for the prevention and treatment of induced neutropenia following chemotherapy [19]. It can also reduce the risk of neutropenia with or without fever during chemotherapy, reducing the incidence of infection, reducing the need for antibiotics and accelerates the recovery of neutrophils [20-24].

It is worth noting that in the recipient patient, the need for chemotherapy reduction dose or its delayed was decreased [25, 26]. Neulasta is also pegilated form of G-CSF or PEG-Filgrastim. The Neupogen produced by Amgen in 1991 and approved by the American Food and Drug Administration as a preventing drug for cancer patients after chemotherapy, Swiss company “Roche” has been licensed to sell the two drugs since 1989, In various countries, including the Middle East countries, it was reassigned to Amgen from January 2014 [27, 28].

Lonograstim is another human recombinant form of granulocyte growth promoter that is made in Chinese hamster ovary cells [29]. The American Society of clinical Oncology (ASCO) first published a guide to using these factors in 1994. The guidelines for primary prevention (in the first cycle), indicate drug administration when the risk of predicted fever

and neutropenia after chemotherapy was greater than 40%, although it was changed to 20% in 2006 [30, 31].

In 2007, the Journal of Clinical Oncology of the United States survey results of 17 trials on 3493 cancer patients after receiving chemotherapy and confirmed the reduction in fever and neutropenic mortality following infection after GCSF in order to prevent its side effects [25].

In contrast, in the same year, another study was conducted that examined the results of 148 experiments and did not affect the growth factor in similar conditions in reducing mortality in patients. In the event that the incidence of infection was reduced following the use of this factor [32].

در مقابل در همان سال، مطالعه ای دیگر انجام شد که به بررسی نتایج ۱۴۸ کار آزمایی انجام شده پرداخته بود و هیچ تاثیری برای فاکتور رشد در شرایط مشابه در کاهش مورتالیتی بیماران قائل نبود. در صورتی که کاهش بروز عفونت را به دنبال مصرف این فاکتور را محرز می‌پنداشت[۳۲].

From October 2005 to September 2014, a recent update on the use of this factor was released in July 2015 by the American Society of clinical oncology. From the cases that could be mentioned, the use of factors The stimulant for the growth of blood colonies is to prevent, when the risk of fever and neutropenia is greater than 20%, and there is no alternative treatment protocol that does not require this factor.

با بررسی های انجام شده بر روی مطالعات مختلف توسط انجمن کلینیکال انکولوژی امریکا از اکتبر ۲۰۰۵ تا سپتامبر ۲۰۱۴ آخرین نسخه به روز رسانی شده در ارتباط با مصرف این فاکتور در جولای ۲۰۱۵ منتشر شد.از مواردی که می توان به آن اشاره کرد استفاده از فاکتورهای محرک رشد کلنی های خونی به منظور پیشگیری، هنگامی که خطر بروز تب و نوتروپنی بیشتر مساوی ۲۰٪ باشد و هیچ پروتکل درمانی جایگزینی که نیاز به این فاکتور نداشته باشد ،موجود نباشد.

Also, in early prevention, when considering the patient's condition (age, the nature of the disease, the chemotherapy regimen required and etc.) that the risk of fever and neutropenia is high, using the Dose-Dense chemotherapy regimen that requires this factor should only be limited to clinical trial studies that are appropriately designed and supported by useful and effective data and information. Also, use of this factor is approved for patients exposed to whole body deadly radiation in radiotherapy [33].

PEG-Filgrastim is a long-lasting form of filgrastim, which made by adding polyethylene glycol to the amine group (pegilation process) of filgrastim. Increasing the size of the molecule and caused by reducing the renal clearance and overcoming the neutrophilic clearance in the removal of the drug and increased the half-life of the drug from an average of 3.5 to 42 hours. The main advantages of this drug need to be administered once in each chemotherapy cycle with the same level of biological activity (binding to the same receptor and stimulation of proliferation and differentiation of neutrophils) with filgrastim. Neulastim is the reference brand of PEG-Filgrastim [12].

TinaPeg is manufactured by Aria Tina gene and all quality control products are being tested on it and their results indicate that it is satisfactory and comparable to the Neulastim

product. The aim of this study was to prove the therapeutic efficacy of this drug with the reference product in terms of the incidence of neutropenia, the severity and duration of fever and neutropenia after chemotherapy.

At the beginning of the literature review, we did not found any publication in the country that comparison of PegFilgrastim with Filgrastime.

The pharmacokinetics of PegFilgrastim were evaluated in 379 patients with cancer. Clearance is nonlinear and decreases with increasing the dose. Bonding to the neutrophil receptor is an important part of PEG clearance. Therefore, it is directly proportional to the number of neutrophils, and weight is also a major contributor to the fact that patients with higher weights with PEG exhibit more systemic exposure. The half-life of Neulastim varies from 15 to 80 hours, with an average of 40 hours [13, and 14]. The pharmacokinetics of PEG do not affected with sex, age, and renal function.

In 35 children with sarcoma (15) 100 mcg / kg Neulastim, the following half-lives were achieved in different age groups:

0 to 5 years (12 people): 30.1 (± 38.2) hours

6 to 11 years (10 people): 20.2 (± 11.3) hours

12 to 21 years (13 people): 21.2 (± 16.0) hours

Charles L. Vogel et al. compared the effect of PegFilgrastim in reducing neutropenic fever, in differant centers (multicenter) with placebo in patient with breast cancer. In 463 patients, 6 mg of PegFilgrastim was given on the second day of each 21-day cycle and 465 patient recived placebo. Patients in the PegFilgrastim group had fever and neutropenic fever (1% vs. 17% with $p < 0.001$), less incidence of neutropenia (1% vs. 14% with $p < 0.001$) and requiring less antibiotics (2% vs. 10% With $p < 00.1$) [16].

Concomitant use of PegFilgrastim and chemotherapy drugs reduces fever and neutropenic levels significantly, resulting in neutropenia and antibiotic use.

Green and colleagues compared the effects of PegFilgrastim in single-dose therapy with filgrastim daily in adults with stage two, three or four of breast cancer in their clinical trials. In this multi-centered operation, 152 patients were randomly assigned to one of the two treatment groups [17].

The primary outcome was the duration of grade four neutropenic (absolute neutrophil counts less than 500 per cubic millimeter) in cycle 1 chemotherapy. The mean of elapsed days with Grade 4 neutropenia in two treatment groups and during 4 cycles of chemotherapy was not statistically significant. During the duration of the study, the incidence of fever and neutropenia in the PegFilgrastim group was about 13% and in the Filgrastim group was about 20%, and the difference was not statistically significant.

Julie M. Vose et al. Compared the effect of single-dose PegFilgrastim (100 μg / kg) with Filgrastim 5 μg / kg daily, in neutropenic prophylaxis in patients with Hodgkin's and non-Hodgkin's lymphoma who were resistant to conventional chemotherapy treatments and treated with Salvage chemotherapy (multicentral open lables Clinical trial study). Grade 4 neutropenia was found to be 69% in the PegFilgrastim group and 68% in Filgrastim and also in the duration of neutropenic durations (2.8 days in comparison with 2.5 days). Therefore, a single injection of PegFilgrastim 100 μg / kg for continuous serum levels with daily infusion of filgrastim (an average of 11 injections) produces a similar effect in terms of its effect and side effects [18].

In 2012, in Europe's G5 countries, the cost-effective use of 300 μg filtrate (Neupogen and the similar form, Zarzio) was compared with PEG-filgrastim, Neulasta, 6mg for prevention and treatment of febrile neutropenia in the range of 1-14 days, as well as the superiority comparision of filigreetis 300 μg of zarzio with 300 μg Neopagene. Neopagene treatment costs € 128.16 per day (€ 1794.30 per 14 days) compared to Zarzio € 94.46 per day

(€ 1336.46 per 14 days). Neulasta reverses its benefits on the twelfth day of Neopagan treatment, while on Zarziu on the fourteenth day Zarzio is preferable to neopagene and neolasta at a cost benefit. Therefore, in the absence of compelling reasons for the pharmacological benefit of PegFilgrastim, there is no reason to use Neulasta instead of Zarzio, and Neulasta's benefit to Neupogen is limited in terms of cost-benefit. The short interval is three days [19].

L. Castagna et al. Compared the effects of PegFilgrastim with Filgrastim after high dose chemotherapy and autologous stem cell transfusion (Open labels randomized clinical trial).

Eighty patients were divided into two groups of 5 µg / kg Filgrastim daily and PegFilgrastim (6 mg), one day after receiving the stem cells, and the duration of neutropenia and the time to neutrophil count was higher than 109 ± 0.5 where mentioned. The duration of neutropenia in the FIL and PEG groups was 6 days and 6.2 days, and the neutrophil reaches a peak of 10.5 ± 10.5 was 11.5 versus 10.8 days, with a difference in mean neutrophil reaches greater than 109.0 ± 1.0 (12.2 days versus 12 days). The prevalence of fever (62% vs. 56%) was not proven (31% vs. 25%).

The mean time of treatment with antibiotics was 5.7 and 4 days in the FIL and PEG groups, respectively. The result indicated that PEG was not as effective in the regeneration of blood cells as FIL, and was an appropriate alternative after high dose chemotherapy and autologous stem cell injection.[٢٠]

Harold J. Burstein and colleagues approved the AC chemotherapy protocol in breast patients as doxorubicin / cyclosporine 60/600 mg / m2 cycles, followed by four cycles of

paclitaxel 175 mg / m^2 two weeks with 6 mg PEG injections on the second day Each cycle, as well as Darbepoetin alfa 200 g subcutaneous every two weeks in hemoglobin, was less than 12 in 135 patients, and the rate of fever and neutropenia and the need for Pessel transfusion significantly decreased (cohort study).[۲۱]

Kourlaba G et al., evaluated the prophylactic effects of single-dose pfg-filtration and on-time filgrastim in febrile neutropenia (FN), severe neutropenia (Grade 3 and 4) delayed treatment and decreased doses (more than 10%) in breast cancer patients receiving chemotherapy regimen Adjuvant compared with doses dense. 3.4% FN was reported in the FIL group and 4.3% in the PEG group, more than half of which occurred in the first four treatment sessions. Compared to the PEG group, patients receiving FIL were three times more likely to have severe neutropenia, resulting in lower doses, but no difference was observed in the incidence of FN in the two groups. Therefore, patients receiving PEG had significantly less severe neutropenic doses and delayed treatment (retrospective cohort study) .[۲۲]

In the search for data in international databases, in addition to the results of the clinical trials of phases 1 and 2 of the granulocytic growth stimulus factor between 1989 and 1998, Phase 3 clinical trials were conducted on patients with various cancers , Has been limited, almost since 1995. It is quite natural that the initial trials were non-random or Open-label, but with time, more standard designs of these trials were randomized with the control group (with or without placebo) and double-blind.

One of the first two-blind randomized clinical trials by Gogwin et al. (1998) was conducted on elderly patients with acute myeloid leukemia. 255 patients aged 55 years or

older with this malignancy were randomly assigned to either the chemotherapy protocol or placebo (control group), and in the other group the same protocol with G-CSF with 400 μg / m^2 surface area. The drug was injected intravenously within 30 minutes and once a day during the course of chemotherapy. Regarding the total response index, the two groups did not differ significantly (in the placebo group 50% and in the G-CSF group 41%), and in terms of the mean overall survival score, the two groups had the same status as the response index, which was statistically significant it was not significant (9 months in the placebo group versus 6 months in the G-CSF group), but in terms of the duration of time needed to improve the neutrophil status, the G-CSF group was 15% shorter than the placebo group This difference was statistically significant. However, the use of G-CSF did not reduce the incidence of all infections and also the incidence of fatal infections, but the duration of infection and the need for antibiotics in the G-CSF group was lower than that of the placebo group, which statistically means [34].

Thatcher et al. (2000) evaluated the effectiveness of Len-Grastim's G-CSF in improving the survival of patients with small cell lung cancer, in the framework of the multicenter clinical trial of the British Medical Research Council. In this trial, 403 patients with this cancer were randomly assigned to control (group C) and G-CSF (group G). Group C was treated with the protocol of the three chemotherapy drugs, doxorubicin, cyclophosphamide and autopsy every three weeks for 6 cycles, and the G group was treated with the same protocol, with a higher 50% dose, every two weeks plus Lenograstim [35].

The findings of this multicentre study showed that the overall response rate in the G group was 40% and in the C group was 28%, which was statistically significant. Also, the survival rate in the G group was better than the C group (hazard ratio or 0.99 with a 95% confidence interval between 0.65 and 0.99).

Garsia-Carbonero et al. (2001) evaluated the effectiveness of G-CSF therapy in a multicenter clinical trial on cancer patients with high-risk fever and neutropenia. 210 patients with a type of solid tumor that were followed by conventional chemotherapy protocols with grade 4 fever and neutropenia were randomly assigned to one of two groups of Ceftazidime antibiotics plus amikacine without G-CSF (control group) and with G- CSFs were dosed at 5 µg / kg daily (intervention group). The mean duration of grade 4 neutropenia in the G-CSF group was two days and in the control group 3 days ($p < 0.05$). Also, the mean duration of hospitalization was 5 days in the G-CSF group and about 6 days in the control group, which was statistically significant.[۳۶]

Del Giglio et al (2008) in Phase III clinical trial to evaluate the superiority of the drug XM02 than placebo and equally effective drug Neupogen reducing the incidence of severe neutropenia, febrile neutropenia in breast cancer patients receiving the regimen Doxorubicin / Docetaxel's [37]

348 patients in 10 countries and 52 centers in 3 groups (2.2.1) were divided into three groups: placebo (72) neupogen (136) and (140) XM02. Filgrastim with a dose of 5µg / kg / day was injected after chemotherapy for a minimum of 5 days and a maximum of 14 days. The difference was between the two treatment groups (0.028 days), which was within the same range.

The incidence of fever and neutropenia in the first cycle was approximately equal in the neupogen group (12.5%), XM02 (12.1%), and about 1/3 of the placebo group (36.1%). The increase and decrease in absolute neutrophil counts was similar in the two drug groups. To evaluate the safety of the drug, the side effects of the drug were studied in three groups: bone

pain and weakness were reported with a higher incidence, the incidence of which was similar in the two drug groups.

Patients in the placebo group received XM02 after the completion of the first chemotherapy and the severity of neutropenia, neutrophil counts, and mean recovery time of neutrophils as the result of a secondary variable were compared, in all cases, the drug biosimilarity with a reference drug were indicated.

Waller et al. (2010), in the third phase of a double-blind, multicenter trial in Europe, examined the equivalence of the Nivestim drug manufactured by Hospira against the Amgen filgrastim in chemotherapy recived breast cancer patients. In this study, 279 patients were enrolled in 201 patients in two groups: Nivestim (184) and Neupogen (95 patients). Filgrastim was injected subcutaneously at a dose of 5µg / kg / day from day 2 to a maximum of 14 days per cycle. The primary endpoint, severe neutropenic time was defined in the first cycle, which was calculated in the neupogen group 1.3 days and the Nivestim group was 1.6 days (95% CI), which proved the drug equal to each other. As secondary variables of the study, the duration of severe neutropenia in the second and third cycles, the duration of neutrophil recovery and the incidence of fever and neutropenia in the first to third cycle were calculated [38].

There were no significant changes in laboratory parameters in the two groups. The results for fever and neutropenic examination were approximately equal (12.57% -12.63%) in the Nivestim and Neupogen groups, as well as adverse effects of Nivestim and Neupogen in the same proportion (86.9% versus 84.2%), respectively [38].

There was no statistical difference between the two groups in terms of hospitalization due to fever and neutropenia, and since no anti-drug antibody was detected in any disease, in 2010, this drug was approved by EMA, as with all filtration referral applications.

Beksac et al. (2011), in their open-label multi-center clinical trial conducted in the framework of Turkey's leukemia study, randomly divided 260 patients with acute myeloid leukemia with neutrophil less than 500 per cubic of millimeter into treatment groups The usual chemotherapy for Induction (the control group), the treatment for Induction chemotherapy, plus Filgrastim or Neupogen, from Roche Inc. (intervention group). The underlying variables of the two groups were similar at the beginning of the study. Overall therapeutic response was not significantly different between the two groups. However, the median duration of hospitalization in the Neupogen group was 4 times less than that of the control group (31 days versus 35 days), but this difference was not statistically significant. In the weekly follow up of patients, the white blood cell count at the end of the first week was similar in two groups (median 700 / mm 3), but at the end of the second, third and fourth weeks, the status of this index was better in the Neupogen group than in the control group. The last follow-up, or the fourth week, of the difference between white blood cells in the two groups was statistically significant (3200 per cubic millimeter in the Neupogen group versus 1800 in the control group) [39].

Ruiz et al. (2011) in Cuba, during the fourth phase of a clinical, non-randomized, and openlable trial, examined the efficacy and safety of LeukoCIM in neutropenic patients following chemotherapy. 47 patients who experienced 95 neutropenic episodes during the treatment were enrolled (retrospective observational study). They divided the patients into two groups on the basis of a filtrated regimen for treatment or prevention. In this study, the delay or delay of the next cycle of chemotherapy was defined as the main response variable.

Statistically, there was no relationship between the main response variable and the type of group (prevention or treatment) (80.7% - 84.2%). The mean absolute count of neutrophils at start and end was (1.4590-1.551 / ml) and the maximum time to improve neutrophil status was calculated one week. Therefore, 82.1% of patients received the next cycle of chemotherapy without delay. In this way, the efficacy of this product, like other granulocyte growth promoters, was reported. Safety of the product was also investigated by studying side effects. The most commonly reported adverse drug reactions were fever (11.22%) and bone pain (11.22%), which is a known and commonly found complication of filigrastim [40].

In a multi-center and non-randomized study of safety in Japan, Sagara et al. (2013) examined the efficacy of Fsk0808 (filgrastim) in breast cancer patients. In this study, 104 patients were enrolled in 6 chemotherapy cycles (413 total cycles), which was the outcome of the initial variance; mean Graphet neutropenic grade 3 was defined in the second cycle, which was calculated as 2.2 days (105: SD) (97 %: One-way CI 2.2 days) [41].

The secondary outcome variable was defined as the incidence of fever and neutropenia and Anti GCSF antibody tracking, which was reported as 34.6% and (0) respectively. The most commonly reported side effects were back pain (60.6%) and bone pain (9.6%).

The findings of this study showed that this drug is well tolerated by patients and can effectively stimulate neutrophil status in patients with breast cancer under chemotherapy [41].

Blackwell et al. (2015) compared a study of EP2006 and neupogen in breast cancer patients who received chemotherapy to prevent neutropenia. Phase III study was a double-blind, randomized clinical trial in 25 of the 218 patients. Patients were divided into four groups (1.1.1.1), two alternating and two non-alternating groups. Patients in the non-

intermittent group received neupogenes or EP2006 chemotherapy cycles, and in the alternating group, the drug was changed in each cycle.

Filgrastim was injected from day 2 of each cycle up to a maximum of 14 days at a dose of 5μg / kg / day. The duration of severe neutropenia (the outcome of the primary efficacy variable) in the neupogene group (with 105 patients) or EP2006 (with 101 patients) was the order of (1.02 ± 1.20 and 1.11 ± 1.17) (97%, CI) was reported that did not show significant difference [42].

Drug safety was investigated by examining the side effects and Anti GCSF antibody secretion. In the first cycle, side effects that were probably related to filgrastim were reported between the Neupogen (19.6%) and EP2006 (20.6%) groups. Antibody production was reported as zero. The drug was approved by the US Food and Drug Administration in March 2015 and was introduced as the first Neupogen biochemical drug in the United States [43].

In the search for internal intelligence sources, there were two reports of clinical practice on this growth factor. Moafee et al. in a cross-over, double-blind randomized clinical trial, therapeutic effects and effects of granulocyte stimulator growth factors. The construction of a domestic company called PD-Grastim with Neupogen, the Amgen plant (as standard treatment) in children they compared the types of cancers that were 1-15 years old [44]. In each of the treatment groups, 30 eligible children received a PD-Grastim or Neupogen treatment for 4 days at the end of their current chemotherapy treatment, and according to the nature of the crossover design, in the next period of chemotherapy, treatment The other was applied to each child. The mean number of white blood cells, neutrophil count and the mean absolute number of neutrophils in the two groups were almost the same and did not differ

significantly. Hospitalized due to fever and severe neutropenia occurred in 3 patients in the Neupogen group and 4 in the PD-Grastim group, but no statistically significant difference was observed between the two groups. In this study, the reference to the wash-out period was not used to clear the effect of the first drug used and then the onset of the next therapeutic period, which is related to the general principle of purifying the effect of the medication on the body over 7 times the half-life of each drug [45], which is half life of the filgrastim drug, ((T1 / 2 = 3-4 h) [46].

In Hoffman's study, the use of neolastine was widely used in patients with non-Hodgkin's lymphoma, which began in Colombia and Mexico in 2016, to patients subjected to a constant dose of 6 mg subcutaneously 24 hours after three weeks of chemotherapy randomized CT or ICT protocols were used for treatment [47].

Another similar study done by Ehsani et al. In Bahrami's Children's Hospital in 8 children under the age of 16 with neuroblastoma was compared to the efficacy and side effects of two filgrastim drugs manufactured by the American Amgen plant (Neupogen), similar to the Iranian PD- Grastim [48].

In a cross-over study, Dr. Yoosefian et al. Compared the effect of filgrastim and pegfilgrastim in the treatment of 33 patients under the age of 16 underwent neutropenic therapy. As a consequence of the variable of study, absolute neutrophil counts are evaluated one week after medication and side effects within 7 days [48].

Another study by Dr. Hemayee et al. Compared the efficacy and side effects of filigrastim produced in the country and neopagene. 168 patients with breast cancer were divided into two groups and the study was designed in parallel. Complications, duration of neutropenia and neutropenic abnormalities were evaluated between the two groups [48].

Dr. Razavi and his colleagues examined the efficacy, safety and tolerability of the filgrastim and PEG-filigrastim product in the country compared to neupogen drug in preventing chemotherapy-induced neutropenia. 21 patients with breast cancer were randomly divided into 3 equal groups. Various parameters including the number of days of severe neutropenia, neutropenic neutropenia, laboratory test dysfunction and side effects were indicated as initial variable [48].

Dr. Salimi et al. Compared the therapeutic effects and adverse effects of filgrastim in the manufacture of domestic and foreign partners in neupogen in patients with gastric cancer. 60 patients were enrolled and measured white blood cells, hemoglobin and platelets after medication intervention as initial variable [48].

The primary outcome was neutropenic fever with absolute neutrophil counts of less than $5*10^9$ and fever equal to or greater than 38 degrees of celsius. The age of the patients was 18-65 years and in both genders. The US National Library of Mediciue, in a trials, compared the efficacy and safety of biosimilar pegfilgrastim in high-risk breast cancer after chemotherapy and reported it in 2016. In a Phase 3 randomly Blind, parallel and multicentre study, blind groups of 180 adult breast cancer patients in stage 2-4 were treated in Brazil with a maximum of 4-21 days chemotherapy regimens. Comparison between neulastim and PEG-filgrastim europharma was performed. The initial outcome was the duration of severe neutropenia in 21 days of the first chemotherapy session. This review was conducted by the Eurofarma S.A laboratory [48].

The pegfilgrastim is composed of filgrastim (G-CSF recombinant human methionine) with 20kD polyethylene glycol (PEG) bonded to the N-methionine terminus in the form of

quantification. The filtration is produced in the form of recombinant DNA technology from E.coli (K12).

Neulastine is a clear, colorless solution, and used to reduce the neutropenia and neutropenic fever in patients undergoing cytotoxic chemotherapy for malignancies, with the exception of chronic myeloid leukemia and plastic myelodysplastic syndrome. It administered in any chemotherapy cycle as a one dose of 6 mg subcutaneously, 24 hours after chemotherapy [49].

In children and young people under the age of 18, Neulastim has not been recommended. Also, in individuals with a high sensitivity to pegfilgrastim, filgrastim and proteins produced in E. coli. Precautions for the use of neulastim or pegfilgrastim: This drug should not be used to increase the dose of chemotherapy. It has also not been studied in patients with high chemotherapy doses. Sensitivity: The induction of anaphylactic shock that occurs initially or after use, or history of excessive hypersensitivity to it, should not be prescribed [50].

In terms of immunity, bone pain is generally mild to moderate, and is controlled in many patients with housing. Most of the unwanted side effects are bone pain and muscle aches. In two randomized, double blind studies in 2 to 4 breast cancer patients under the chemotherapy regimen with Doxorubicin and Docetaxel, using a single dose of pegfilgrastim in any chemotherapy cycle, a decrease in neutropenic dose and a similar reduction in neutropenic fever were observed using daily filgrastim administration. The results were reduced to 4 neutropenic gradients for 5 to 7 days and 30 to 40% reduction of neutropenic fever. In the first study, in 157 patients using 6 mg pegfilgrastim, the reduction in the duration

of neutropenia was 8.1 days, compared with 1.6 days in the filgrastim, and the neutropenic fever was 13% in Pegfilgrastim and 20% in filgrastim [50] .

In the second study, in 310 patients, the mean neutropenic gradient 4 period was 1.7 days with pegfilgrastim and 1.8 days for filgrastim. The reduction in neutropenic fever was 9% in pegfilgrastim and 18% in filgrastim. In a study comparing the use of placebo and the effect of pegfilgrastim on reducing the neutropenic fever that occurs in 10-20% of patients, 928 patients were randomized to single-dose pegfilgrastim and placebo groups 24 hours after chemotherapy. Neutropenic fever in patient's tht recived pegfilgrastim was significantly rediuced and the duration of admission and the need for treatment of neutropenic fever were also significantly decreased. By administering a dose of pegfilgrastim, maximum serum concentrations are reached 16 to 120 hours after injection [50].

Removal: Removal of pygfilogram is not linear; its clearing is reduced by increasing the dose; about 99% of it is eliminated by neutrophil. Also, with the self-regulating mechanism, the concentration of serum pegfilgrastim decreases with the onset of neutrophil recovery.

Safety Data: In a 6-month toxicity study, subcutaneous injection once a week, 1000 micrograms and 23 times more than the human dose was performed in the rat, and no cancerous or pre-cancerous lesions were observed.

goals of study:

• Comparison of prophylactic and therapeutic effects of TinaPeg with Neulastim in terms of duration of severe neutropenic duration in breast cancer patients

• Comparison of prophylactic and therapeutic effects of TinaPeg with Neulastim for the incidence of febrile neutropenia in breast cancer patients

• Comparison of TinaPeg's effects and prophylaxis and therapies with Neulastim for the duration of severe neutropenic duration in breast cancer patients according to the underlying variables such as age and severity of the disease

• Comparison of adverse events such as bone pain in the two treatment groups TinaPeg with Neulastim and the effect of variables such as age and severity of the disease

• The prophylactic and therapeutic effects of TinaPeg and Neulastim are not different from the primary and secondary outcome indices.

Side effects profile observed in the two groups of TinaPeg and Neulastim, have no significant difference

Primary goals: Evaluation of the prophylaxis and therapeutic effects of TinaPeg with Neulastim on the absolute count of neutrophil counts after chemotherapy in patients with breast cancer

• Secondary Objectives: Comparison of Prophexal and Therapeutic Equivalence Effects of TinaPeg with Neulastim for the Indicator of Severe Neutropenia Duration in Patients with Breast Cancer

• Comparison of the effects of prophylactic and therapeutic equivalence of TinaPeg with Neulastim on the incidence of Febrile Neutropenia in breast cancer patients

• Comparison of the effects of prophylaxis and healing of TinaPeg with Neulastim in terms of duration of severe neutropenic duration in breast cancer patients according to the underlying variables such as age and severity of the disease

Methodology of study

Study Description:

Study design and reasons for selecting a control group:

In this study, the two groups of 51 women with breast cancer who were randomly assigned to one of the treatments were statistically analyzed.

Condition of the population studied:

The study population was women over the age of 18 who had been approved by a fellow physician with breast cancer and had criteria for entry into the study.

Criteria for entering the study:

1. The definitive confirmation of breast cancer diagnosis with pathology

2- Stage 1-4, which requires a chemotherapy with an AC regimen based on the NCCN guide line.

3. Age over 18 years

4) Women with a possible pregnancy should be prevented from using their appropriate contraception during the course of chemotherapy (using a safe contraceptive method). Postmenopausal women who have at least 12 months of menopause do not need prenatal care.

5. Not having symptomatic infections and fever with the approval of a peer-reviewed physician

6. Activity of the red bone marrow that is defined as follows:

Leukocytes> / = 3000 / μl

Absolute neutrophil count > / = 1,500 / μl

Hemoglobin > / = 8.0g / dl

Platelets > / = 100,000 / μl

Total bilirubin and serum creatinine must be <1.5 mg / dl

4 chemotherapy courses will be rehab.

8. Patients have the ability to read and understand the form of participation in the study and can independently and with knowledge be able to decide to participate in the study and sign a consent form.

Non-inclusion criteria:

1. The patient has recently undergone systemic chemotherapy.

2. The patient has undergone a major surgery in the last 4 weeks.

3. A history of uncontrolled seizures, coma and mental disorders, and any other disorder that the investigator finds to prove that the patient is not qualified to decide and sign a consent form.

5- Pregnant or breastfeeding patients to your child.

Exit criteria:

1- Do not continue to treat for personal reasons during the study.

2. During the study, you have complications that can not continue to be treated.

3- During the study, show severe allergy to treatment and drug injection.

4. During the study, it should be noted that she did not have one or more entry conditions.

5. During the study, lose one or more of the conditions of entry in the study.

6. During the study, it should be determined that one or more of the non-arrival conditions have been ill.

7. During the study, the patient will die.

Interventions:

In this interventional study, injection of pegilated granulocyte stimulating factor (PEG-GCSF) tinapeg, produced recombinantly in the Aria Tina gene, and neulastime, an external brand, was used to treat women with breast cancer and the criteria for entering the study listed in the above are. Drug injection was performed 24 hours after any chemotherapy cycle in the designated centers. The pegylated granulocytic stimulus (6 mg) was injected as a single subcutaneously dose.

All patients with breast cancer with stage 1-4 were initially entered into a "Run-in-period". At this stage, a collaborator physician visited all patients and, in terms of entry criteria and lack of entry, obtained the necessary assurances, and if some paraclinical examinations of the patients were incomplete, they requested those tests to decide whether to enter or Patients will not be allowed to arrive at a certain degree. Subsequently, adequate descriptions and training were given to the patient by a respected expert, and then the informed consent form was completed by the patients.

Effects and safety implications of the study:

Data management

In order to monitor data and related issues (DSMB) Safety and evaluate the progress of the clinical study, safety information, significant outcomes of effectiveness and decision making regarding the assessment of adverse event occurring during the conduct of a committee study consisting of the main researcher Dr. Mousavi, counselor The statistics were compiled by Dr. Keshtkar and Dr. Afshari, the representative of the company, and Dr. Shahi and Dr. Mirzanya (independent from the study).

Statistical Methods, Model Analysis and Sample Size:

In this study, the two-way one-sided test (TOST) was used according to the equivalence trial and based on the following resources (two references 28 and 29). In this method, we compare the equivalence margin (conventionally equivalent to σ), which was previously determined with an interval equal to 100-2α. To better understand this concept and subject, see Figures 1 and 2 (section of images). When the findings of this study confirm the equality or equivalence, both the upper and lower bounds of the confidence interval (100-2α) of the difference in the therapeutic effect in the two groups are in the range or interval [-σ ~ +σ] . So in other words, if in this study, the level of error of the type I or alpha is 0.05, then the 95% confidence interval was first determined for the difference in the effects of the two treatment groups in this trial (confidence interval 95% difference between the mean neutrophil count and this interval is within the range of -200 to +200, then the equality of the two treatments being studied is acceptable, and in the other range of this decision, if any other state, one of the two lower or upper bounds, is outside the range was the same, the equality of the two treatments is not fixed. In this situation, if the point estimation of the "mean difference" index of absolute neutrophil counts between the two treatment groups is within the range and the lower and upper bounds of the 95% confidence interval are outside the above range, the statistical power of the result The result is calculated to allow comparing the calculated power

with the minimum power or even the desired power (that is, equal to 80% and 90% respectively).

Because in the proposal for this trial, margin was defined as equivalent to 200 neutrophils for proof of equality, therefore, this threshold was used to evaluate and analyze the relevant statistics, so that the statistical analysis performed in this study was based on the state of "initial statistical analysis" or Primary Analysis, and all results based on this analysis (either p value or estimated effect size) are considered to be Conclusive or Concirmatory Results [51-52].

On the other hand, the evaluation of data related to the initial outcome of this trial showed the following facts:

• Distribution of absolute neutrophil counts is an irregular distribution, and the evaluation of different central and dispersion indices, graphic pattern (using the histogram diagram) and also the result of the Kolmogorov-Smirnov test indicate the abnormal distribution of this variable.

• The variance dispersion index or the standard deviation of the initial outcome is strongly influenced by the maximum values (overt data) (Fig. 1), and due to the strong increase in the dispersion index of this size or error, the criterion of the difference in mean values leads to widening of the interval 95% confidence is the most important decision in the main goal of the trial (Mean Difference).

• Considering repeated or repeated measurements of the main outcome and other important blood markers in each Repeated Measures Design, since there are no significant changes in the central indexes of the main outcome in the second and third cycles, The ability to design repeated measurements to pre-post design (Before-After / Pre & Post Design).

Obviously, the most important measurement cycle is the main outcome, the last cycle or the fourth cycle, and in this case, the recommendation of most trial methodologists is to consider the distribution status of the outcome in the first measurement or baseline as an effective factor in statistical analysis. . In particular, the comparison of the mean total neutrophil count in the first measurement (in the first cycle) indicates a difference of about 350 neutrophils, which is approximately equal to 2 times the margin or threshold defined. It needs to be explained that in these common designs in most trials, the following three commonly used statistical analysis tools are used: Option 1: Mean of Change Comparison or Comparison of the Average Outcome Changes in The second option is to compare the relative changes in the Mean of Relative Changes, which is, in fact, the comparison of the percentage of changes in the number of neutrophil counts and the third option: total intra-group comparisons Two comparisons, each for each group) and two intergroup comparisons (at both the first and fourth cycle times, separately), each of the comparisons Above, in the trials of two groups using independent t-tests (or option nonparametric equivalent, the Mann-Whitney) do lie [52-53]. However, experts in methodology and bioinformatics (led by Professor Douglas Altman and his colleague Professor Martin Blund for the first time), for the sake of good reason, have warned practitioners of these preeminent approaches and jointly opted for "the use of models Analysis of variance-covariance "[54-56]. Obviously, the quantitative outcomes in the base phase as covariance, the treatment groups, as a factor (independent variable) and a quantitative outcome measure at the last time of the study, will be considered as a dependent variable.

Given the above three considerations and the need for an analysis of the evaluation of the therapeutic effect of equality, based on the primary outcome (the main consequence) of the absolute count of neutrophils, use statistical methods / methods to achieve this goal, which

is the validity of the results or findings. The results of these methods are not distorted. So, in this section, we refer to six approaches or statistical analysis models (with the headings of approaches A to F), and then we will mention the findings of each of these approaches:

شیوه های آماری, مدل تحلیل و حجم نمونه:

در این مطالعه با توجه به منطق equivalence trial و براساس منابع زیر (دو رفرنس مورد اشاره ۲۸ و ۲۹) از روش بسیار معمول Two One-Sided Test (TOST) استفاده گردید. در این روش مارژین برابری یا Equivalence margin (بطور قراردادی آنرا معادل σ در نظر می‌گیریم) که قبلاً تعیین شده با یک بازه که برابر با 100-2α است مقایسه گردید. برای درک بهتر این مفهوم و موضوع از تصویر ۱ و ۲ استفاده شد(بخش تصاویر). وقتی تصمیم گیری یافته های این مطالعه تایید کننده برابری یا equivalence است که هر دو کران بالا و پایین بازه اطمینان (100-2α) درصد از تفاوت اثرات درمانی در دو گروه، در محدوده یا بازه [-σ ~ +σ] قرار گیرد. بنابراین به عبارت دیگر، اگر در این مطالعه، سطح خطای نوع اول یا آلفا، ۰/۰۵ در نظر گرفته شود، ابتدا فاصله اطمینان ۹۵٪ برای تفاوت اثرات دو گروه درمانی در این کارآزمایی تعیین گردیده (فاصله اطمینان ۹۵٪ تفاوت میانگین تعداد نوتروفیل‌ها) و این بازه اگر در داخل محدوده ۲۰۰- تا ۲۰۰ قرار گیرد، آنگاه برابری دو درمان مورد مطالعه قابل قبول می‌باشد و در طیف دیگر این تصمیم، اگر هر حالت دیگری که یکی از دو کران پایین یا بالا، خارج از محدوده مذکور بود، برابری دو درمان، ثابت نمی گردد. در این شرایط، چنانچه برآورد نقطه‌ای شاخص «تفاضل میانگین» شمارش مطلق نوتروفیل بین دو گروه درمانی، در داخل محدوده مذکور بوده و کران‌های پایین و بالای فاصله اطمینان ۹۵ درصد این شاخص، خارج از

محدوده فوق باشد، توان آماری نتیجه بدست آمده، محاسبه گردیده تا امکان مقایسه توان محاسبه شده، با توان حداقلی یا حتی توان مطلوب (یعنی بترتیب توانهای برابر با ۸۰٪ و ۹۰٪)، وجود داشته باشد.

از آنجا که در پروپوزال این کارآزمایی، مارژین برابری ۲۰۰ عدد نوتروفیل برای اثبات برابری تعریف گردیده بود، فلذا همین آستانه برای ارزیابی و تحلیل آماری مربوطه، مورد استفاده قرار گرفت تا تحلیل آماری صورت گرفته در این کارازمایی از وضعیت «تحلیل آماری اولیه» یا Primary Analysis خارج نشده و همچنین تمامی نتایج مبتنی بر این تحلیل (اعم از p value یا اندازه اثر برآورد شده)، نتایج قطعی یا Confirmatory تلقی گردد [52-51].

از طرف دیگر، ارزیابی داده‌های مرتبط با پیامد اولیه این کارآزمایی، نشاندهنده واقعیتهای زیر بود:

- توزیع شمارش مطلق نوتروفیلها، یک توزیع غیرقرینه بوده و ارزیابی شاخصهای مختلف مرکزی و پراکندگی، الگوی گرافیکی (با استفاده از نمودار هیستوگرام) و همچنین نتیجه آزمون کولموگروف-اسمیرنف، نشاندهنده غیرنرمال بودن توزیع این متغیر میباشد.

- شاخص پراکندگی واریانس یا انحراف معیار پیامد اولیه، تحت تاثیر مقادیر حداکثری (داده‌های پرت) به شدت افزایش نشان داده (نمودار ۱) و از طریق افزایش شدید شاخص پراکندگی این اندازه یا خطا معیار تفاضل میانگین‌ها، موجبات عریض شدن بازه اطمینان ۹۵ درصد مهمترین اندازه در تصمیم گیری هدف اصلی این کارآزمایی (اندازه تفاضل میانگین‌ها یا Mean Difference) می‌گردد.

- با توجه به سنجش‌های متعدّد یا مکرّر پیامد اصلی و سایر نشانگرهای خونی مهم در هر سیکل شیمی درمانی (Repeated Measures Design)، از آنجا که تغییرات شدیدی در شاخصهای مرکزی پیامد اصلی در سیکل‌های دوم و سوم مشاهده نشده است، می توان طراحی سنجش‌های مکرّر را به طراحی قبل و بعد (Before-After / Pre & Post Design) تغییر داد. بدیهی است که مهمترین سیکل سنجش پیامد اصلی، آخرین سیکل یا سیکل چهارم بوده و در این شرایط، توصیه اکثر متخصصین متدولوژی کارآزمایی ها، لحاظ نمودن وضعیت توزیع پیامد مزبور در اولین سنجش یا سنجش پایه، بعنوان یک عامل تاثیرگذار در تحلیل‌های آماری است. بخصوص اینکه مقایسه میانگین شمارش مطلق نوتروفیل‌ها در اولین سنجش (در اولین سیکل)، تفاوت حدود ۳۵۰ عدد نوتروفیل که نزدیک به ۲ برابر مارژین یا آستانه تعریف شده برابری است، را نشان می‌دهد. لازم به توضیح است که در اینگونه طراحی‌های شایع در اکثر کارآزماییهای مختلف از سه گزینه تحلیل آماری زیر، بصورت معمول یا رایج، استفاده می‌گردد: **گزینه اول:** مقایسه تغییرات درون گروهی (Mean of Change) یا مقایسه میانگین تغییرات پیامد در هر گروه با یکدیگر، **گزینه دوم:** مقایسه تغییرات نسبی مقادیر قبل و بعد پیامد (Mean of Relative Change) که در واقع همان مقایسه شاخص درصد تغییرات رخداده در تعداد نوتروفیل‌ها می‌باشد و **گزینه سوم:** مجموع مقایسه‌های درون گروهی (دو مقایسه، هر یک برای هر گروه) و دو مقایسه بین گروهی (در هر دو مقطع زمانی سیکل اول و سیکل چهارم، بصورت مجزا) که هر یک از مقایسه های فوق، در کارآزمایی‌های دو گروهی با استفاده از آزمون‌های تی مستقل (یا گزینه ناپارامتری معادل آن، یعنی یو مان ویتنی) انجام

می‌گیرد[53-52] . بهر حال متخصصین متدولوژی و آمار زیستی (در راس آنها پروفسور داگلاس آلتمن و همکار ایشان پروفسور مارتین بلاند برای اولین بار) با ذکر دلایل متقن، متخصصین کارازمایی‌ها را از این رویکردهای پیشگفت برحذر داشته و بطور مشترک گزینه «**استفاده از مدل‌های تحلیل واریانس-کوواریانس**» را قویاً پیشنهاد نموده اند[56-54]. البته بدیهی است که سنجش پیامد کمّی در مقطع پایه بعنوان کوواریانس، گروه‌های درمانی، بعنوان فاکتور (متغیر مستقل) و سنجش پیامد کمّی در آخرین مقطع زمانی مطالعه، بعنوان متغیر وابسته، خواهد بود.

حال با عنایت به ملاحظات سه گانه فوق و لزوم تحلیل ارزیابی برابری اثرات درمانی، مبتنی بر پیامد اولیه (پیامد اصلی) شمارش مطلق نوتروفیل‌ها، از روش/ روش‌های آماری برای دستیابی به این هدف استفاده نماییم که اعتبار نتایج یا یافته‌های حاصل از این روشها، مخدوش نباشد. بنابراین در این بخش به ۶ رویکرد یا مدل تحلیل آماری (با عناوین رویکردهای A تا F) اشاره نموده و سپس به ذکر یافته‌های هر یک از این رویکردها، خواهیم پرداخت:

✓Model A: Usual Approach: In this statistical method, with the observance of the "prior" principle at the design time of this trial, and despite the challenge of the distribution of abnormal primary outcome, the mean difference index and the standardized standard difference (as the effect size of this Approach) as well as the 95% confidence intervals of these indicators to estimate the equality evaluation. Obviously, in this method, the influential (or somewhat influential) role of the difference in primary outcome distribution in the first chemotherapy cycle (as the basis measure in this trial) is ignored.

 Model B-Routine Approach with Corrected Effect: This approach is similar to the model A approach, and the only difference is that the major factor in the difference between the baseline outcome or the absolute count of neutrophils (during the first chemotherapy cycle) is not ignored and According to the expert advice of the expert expert (see previous sections), the ANOVA / ANCOVA model was used to assess the effect of the desired intervention in comparison with Neolithic therapy (or according to the main purpose of this work, the effect of equality), use It turned out

 Model C-Approach to Using the Mean Ratio Index (Instead of the Mean Difference Index): In the event that the distribution of a quantitative outcome in a two or more trials is abnormal, especially if this distribution can be achieved using The change in natural logarithmic variables converges or converges to normal distribution, at least two positive events occur: first, with this change of variable, the non-symmetric conditions of the distribution of the corresponding quantitative effect are reduced or eliminated and the distribution to the characteristics of a Normal distribution approaches, therefore, the use of some of the most commonly used parametric tests in these trials will not be banned. Because these parametric tests (such as family tests of variance analysis, family linear regression tests, etc.), in contrast to nonparametric tests that only function one-variable, can be in both mono-variable conditions And multi-variable, to evaluate the effects of different interventions. The other positive effect of the change in the variable of this quantitative consequence is that instead of the indicator of the size of the effect of the difference in averages, we can use the ratio of averages indicator, which is also a measure of the known effect in all types of trials of superiority and equality [57]. Mathematically, when a variable value variable is changed from its usual scale to the logarithmic scale, the result of dividing or multiplying the two numerical values of that variable in the usual range is, respectively, equivalent to the sum of the two

values, in logarithmic scale. In other words, because the central index, called geometric mean, instead of calculating the average of the sum of the sum of the values of a variable to the sample number (sample size), first obtains the product of the different values of that variable on the same common scale, and then the The result of multiplication is calculated, the root (radical) n calculates it. Instead of this predefined mathematical operation, we can use the change of the corresponding variable to the natural logarithmic scale, and in this situation, due to the same product of the multiplicative product on the usual scale or sum on a logarithmic scale, we can, on a new scale (logarithmic), be an arithmetic average And the result of this average, if reversed by the mathematical operation of changing the corresponding variable, is converted to the initial scale, then the result is the same geometric mean (the inverse of the mathematical operation of the natural logarithm is to yield the result to the power of e in the mathematical term These operations refer to Exponential. Therefore, with regard to the sum of the issues discussed, in this analytical approach, the challenge of not having a normal distribution of a quantitative outcome is resolved. Another important point in this approach is that it is similar to the approach of using differential averages indices that have threshold or margin equivalents to decide on different interventions tests with different conditions, in this new indicator (the ratio of averages) It is also necessary to have a threshold or margin for assessing the equality of the two interventions. Obviously, differential comparisons of thresholds or margins should be studied on the outcome scale (for example, in this trial, which is the initial outcome, the absolute count of neutrophils, the decision threshold is also based on the same scale, ie, the number) But in the threshold or Margin of equality, in the situation where the decision index is the ratio of the meanings, the absolute number of equality is one (instead of zero in the mean difference index) and this threshold or margin is also around the numerical ratio 1. In reviewing the scientific literature related to the Averages Index, we come to the US Food and Drug Administration's Guidebook, which has

recommended a minimum of 0.8 to a maximum of 1.25 in the 2003 guide to drug biology trials. [58], but these values can not be considered definitive values for all trials. Since neutrophil count is considered equal to the threshold or margin in this study, 200 neutrophils and, on the other hand, if the acceptable level of neutrophil counts of a cancer patient is 2000, then the ratio of this Use two digits, the threshold of 10% on either side of the neutral or null, for this indicator. Therefore, in this study, the two domains in the decision range for this indicator were predicted from a minimum of 0.9 to a maximum of 1.1. This threshold means that when the average neutrophil count in the two groups is considered as the desired outcome, the ratio of the mean neutrophils of the TinaPeg group to the mean neutrophil count of Neulastim patients should not be less than 0.9 and greater than 1.1 (The average neutrophils of the TinaPeg group can be between 10%

- ✓ **مدل A- رویکرد معمول:** در این روش آماری، با رعایت اصل «پیشین» (priori) در زمان طراحی این کارآزمایی و علی رغم چالش توزیع غیر نرمال پیامد اولیه، از شاخص تفاضل میانگین و تفاضل میانگین استاندارد شده (بعنوان اندازه اثر این رویکرد) و همچنین برآورد نمودن فاصله اطمینان ۹۵ درصد شاخصهای مزبور، بمنظور تحلیل ارزیابی برابری، استفاده نمود. بدیهی است که در این روش، نقش تاثیرگذار (یا تا حدودی تاثیرگذار) تفاوت توزیع پیامد اولیه در اولین سیکل شیمی درمانی (بعنوان سنجش پایه در این کارآزمایی) نادیده گرفته شده است.

✓ **مدل B- رویکرد معمول بهمراه اثر تصحیح شده[1]:** این رویکرد مشابه رویکرد مدل A بوده و تنها تفاوت آن این است که عامل مهم تفاوت پایه پیامد اولیه یا شمارش مطلق نوتروفیل‌ها (در زمان سیکل اول شیمی درمانی)، نادیده انگاشته نشده و مطابق توصیه متخصصین خبره کارآزمایی (در بخش‌های قبلی توضیحات مبسوط داده شده است)، از مدل ANOVA/ ANCOVA برای ارزیابی معتبرتر اثر مداخله مورد نظر، درمقایسه با درمان نئولاستیم (یا با توجه به هدف اصلی این کارازمایی؛ برابری اثرات)، استفاده گردید.

✓ **مدل C- رویکرد استفاده از شاخص نسبت میانگین‌ها (بجای شاخص تفاضل میانگین‌ها):** در شرایطی که توزیع یک پیامد کمّی در یک کارآزمایی دو یا چندگروهی، غیر نرمال بوده و بخصوص در شرایطی که بتوان این توزیع را با استفاده از تغییر متغیر[2] لگاریتم طبیعی[3]، به توزیع نرمال تبدیل یا نزدیک نمود، حداقل دو رخداد مثبت ایجاد می‌شود: اول اینکه با این تغییر متغیر، شرایط غیر قرینه بودن توزیع پیامد کمّی مربوطه کاهش یافته یا از بین رفته و توزیع به ویژگی‌های یک توزیع نرمال نزدیک می‌گردد، فلذا استفاده از برخی آزمون‌های پارامتریک پرکاربرد در این کارآزمایی‌ها منعی نخواهد داشت. چرا که این آزمون‌های پارامتریک (از قبیل آزمون‌های خانواده تحلیل واریانس یا آزمون‌های خانواده رگرسیون خطی و ...)، برخلاف آزمون‌های ناپارامتری که فقط کارکرد تک متغیره دارند، می‌توانند در هر دو شرایط تک متغیره و چند متغیره، به ارزیابی اثرات مداخلات مختلف بپردازند. اثر مثبت دیگر متعاقب تغییر

[1]Adjusted Effect
[2]Transformation
[3]Natural Logarithm or Neperian Logarithm

متغیر این پیامد کمّی، این است که بجای شاخص اندازه اثر تفاضل میانگین‌ها، میتوان از شاخص نسبت میانگین‌ها استفاده نمود که این شاخص اخیر نیز یک اندازه اثر شناخته شده در همه انواع کارآزمایی‌های برتری و برابری می‌باشد[57]. از نظر ریاضی، وقتی مقدار عددی متغیری از مقیاس معمول خود به مقیاس لگاریتمی تغییر می‌یابد، حاصل تقسیم یا ضرب دو مقدار عددی آن متغیر درمقیاس معمول، بترتیب معادل تفاضل و جمع آن دو مقدار، در مقیاس لگاریتمی خواهد بود. به عبارت دیگر، دلیل اینکه شاخص مرکزی تحت عنوان میانگین هندسی، بجای محاسبه میانگین حسابی که مجموع مقادیر یک متغیر را به تعداد نمونه (حجم نمونه) تقسیم نماید، ابتدا حاصلضرب مقادیر مختلف آن متغیر را در همان مقیاس معمول، بدست آورده و آنگاه از حاصل ضرب بدست آمده، ریشه (رادیکال) nام آنرا محاسبه می‌نماید. حال میتوان بجای این عملیات ریاضی پیشگفت، از تغییر متغیر مربوطه به مقیاس لگاریتم طبیعی، استفاده نمود و در این شرایط بدلیل همان تناظر حاصلضرب در مقیاس معمول یا مجموع در مقیاس لگاریتمی، می‌توانیم در مقیاس جدید (لگاریتمی) همانند یک میانگین حسابی با آن برخورد نموده و حاصل این میانگین، اگر با عملیات ریاضی معکوس تغییر متغیر مربوطه[۴]، به مقیاس اولیه تبدیل گردد، حاصل همان میانگین هندسی خواهد بود (معکوس عملیات ریاضی لگاریتم طبیعی، این است که حاصل را به توان عدد e برسانیم که در اصطلاح ریاضی به این عملیات، گرفتن Exponential اطلاق می‌نمایند). بنابراین با توجه به مجموع مباحث مطرح شده، در این رویکرد تحلیلی، چالش عدم برقراری توزیع نرمال پیامد کمّی، برطرف می‌گردد. نکته مهم دیگر در این رویکرد این است که مشابه رویکرد استفاده از شاخص‌های تفاضل

[4]Back-transformation or Re-transformation

میانگین‌ها که دارای آستانه یا مارژین برابری برای تصمیم گیری در کارآزمایی‌های مداخلات مختلف با شرایط متفاوت است، در این شاخص جدید (نسبت میانگین‌ها) نیز لازم است تا آستانه یا مارژینی برای ارزیابی برابری مقایسه دو مداخله، وجود داشته باشد. بدیهی است که آستانه یا مارژین مقایسه‌ای تفاضلی، باید در مقیاس پیامد مورد مطالعه بوده (بعنوان مثال در این کارآزمایی که پیامد اولیه، شمارش مطلق نوتروفیل‌ها است، آستانه تصمیم گیری نیز، مبتنی بر همین مقیاس، یعنی تعداد می‌باشد) اما در آستانه یا مارژین برابری در شرایطی که شاخص تصمیم گیری، نسبت میانگینهاست، عدد مطلق برابری، یک بوده (بجای عدد صفر در شاخص تفاضل میانگین‌ها) و این آستانه یا مارژین نیز حول و حوش نسبت عددی ۱ خواهد بود. در مرور منابع علمی مرتبط با شاخص نسبت میانگین‌ها، به دستورالعمل سازمان غذا و داروی ایالات متحده امریکا میرسیم که در راهنمای سال ۲۰۰۳ مرتبط با کارآزمایی‌های دارویی برابری زیستی، قاعده عمومی آستانه یا مارژین حداقل ۰.۸ تا حداکثر ۱.۲۵ را پیشنهاد نموده است[58]، اما این مقادیر را نمیتوان مقادیر قطعی برای تمام کارآزمایی‌ها در نظر گرفت. از آنجا که تعداد نوتروفیل در نظر گرفته شده برای آستانه یا مارژین برابری در این مطالعه، ۲۰۰ نوتروفیل بوده و از طرف دیگر اگر سطح قابل قبول نوتروفیل‌های یک فرد مبتلا به کانسر را ۲۰۰۰ در نظر بگیریم، پس می‌توان از نسبت این دو رقم یعنی آستانه ۱۰ درصد در دو طرف مقدار خنثی یا null، برای این شاخص استفاده نماییم. بنابراین در این مطالعه، دو سر محدوده یا بازه مورد نظر در تصمیم گیری برای این شاخص، از حداقل ۰.۹ تا حداکثر ۱.۱ پیش بینی گردید. این آستانه بدین معنی است که وقتی میانگین شمارش نوتروفیل‌ها را در دو گروه،

بعنوان پیامد مورد نظر در نظر می‌گیریم، نسبت میانگین نوتروفیلهای گروه بیماران TinaPeg به میانگین نوتروفیل‌های بیماران Neulastim نباید از ۰.۹ کمتر و از ۱.۱ بیشتر باشند (یعنی میانگین نوتروفیل‌های گروه بیماران TinaPeg، میتواند بین ۱۰ درصد کمتر تا ۱۰ درصد بیشتر، نسبت به میانگین نوتروفیل در بیماران Neulastim باشند).

 Model D-Approach Using the Corrected Averages Index: This statistical model will also be derived from the previous approach (Approach C), along with correction of the index of the corresponding effect size. Correction method In this model, the use of linear regression on the logarithmic scale is a small initial consequence. It should be noted that the other advantageous alternative to the variable change approach is the small consequence of the absolute counting of neutrophils, that by changing this logarithmic variable, if this new modified result is used in the regression model, by estimating the variable beta coefficient of the treatment group (The treatment is TinaPeg, code 1 and neolastine treatment, as zero), and then returning this factor to the actual scale, in fact the size of the effect of the previous models, the "average ratio" with the 95% confidence interval, It is estimated that it is the same indicator we are looking for in order to assess equality in these situations. Now, using the advantage of the linear regression model in the mentioned conditions, which also allows us to enter other variables, we can measure the initial outcome in the first cycle of chemotherapy (as a baseline measure), albeit on a logarithmic scale (because This variable is common with the initial outcome variable at the time of the fourth cycle of chemotherapy in the absence of normalization) into the linear regression model, and now we can estimate the coefficient of the angle (beta coefficient) of the treatment

group variable, this time the indicator of the effect size The "Adjusted Mean Ratio", with a 95% confidence interval, is estimated. It should be noted that in this approach, in order to evaluate the equality analysis using this predefined index, we would consider the same as C model or approach, threshold or margin equivalence from a minimum of 0.9 to a maximum of 1.1.

 The E-Earning Approach Using the Mean Difference Using the One-Way Pruned Mean: This approach has been used as a "sensitivity analysis" approach. If the main factor out of the distribution of the initial outcome or the absolute neutrophil count of normal vibrancy is due to the extreme effects of overlapping data, especially in the right direction or direction of larger values or positive values of the distribution of this variable, we can use a relatively simple solution And the old one, under the title of "pruned mean" production [58]. In this approach, the percentage of the values in one or both sides of the variable distribution is eliminated and again the average centralized index is calculated. This amount varies from 2.5% to 20%. But since the deletion of data from the initial outcome in terms of the lowest neutrophil count, completely eliminates the validity of the results (because of the deletion or concealment of the drug's lack of effect), therefore, in this approach, only on one side of this variable , A total of 5% of the maximum values were eliminated individually and the corresponding average was calculated again. In these circumstances, this new central index is called the "prime average" one-sided. Meanwhile, some statisticians believe that in distribution-oriented data, distribution distributions are highly positive or right, there is no need for removing or pruning variables on both sides of the distribution, and can only be in the same direction. Maximum values (i.e., the same

direction as the overflow data has caused adverse effects on the variable) can be eliminated [60].

 In this approach (model E), first for the initial outcome, at two stages of cycle 1 and 4, chemotherapy, using their distribution, first, the corresponding point was determined with their 95th percentile, and then the values greater than that of the numerical value of The statistical analyzes performed on the E and F models were eliminated (it should be noted that only the data in this study were excluded in these analyzes). This amount was 7676 and 10800, respectively, for the absolute count of neutrophils at the time of cycle 1 and cycles 4 respectively. Thus, in each of these variables, 5 people were eligible, 2 of whom in this group (in both cycles 1 and 4) in this group were included in this group, These analyzes eliminated 8 people.

 Model F - Approach to using the difference of corrected meanings using the one-way prerecorded mean. This approach is similar to previous approaches, corrected form or format, the previous approach. In other words, in the E model, according to the strict recommendation of statisticians and methodologists of the trials, there is a need to correct the corresponding effect size index, with the corresponding quantitative consequence of the baseline measurement. Also, for the convenience of statistical analysis and ease of extraction of the findings, especially the confidence intervals, a linear regression model was used for multivariate (two independent variables) regression.

✓ **مدل D- رویکرد استفاده از شاخص نسبت میانگین‌های تصحیح شده:** این مدل آماری نیز حاصل رویکرد قبلی (رویکرد C) بهمراه تصحیح شاخص اندازه اثر مربوطه خواهد بود. روش تصحیح در این مدل،

استفاده از رگرسیون خطی بر روی مقیاس لگاریتمی پیامد کمی اولیه می‌باشد. لازم به ذکر است که فایده مثبت دیگر رویکرد تغییر متغیر پیامد کمی شمارش مطلق نوتروفیل‌ها، این است که با این تغییر متغیر لگاریتمی، چنانچه این پیامد تغییر یافته جدید را در مدل رگرسیون استفاده کنیم، با برآورد نمودن ضریب بتای متغیر گروه درمانی (درمان مورد ارزیابی یعنی TinaPeg، بعنوان کد ۱ و درمان نئولاستیم، بعنوان کد صفر)، و سپس برگرداندن این ضریب به مقیاس واقعی، در واقع اندازه اثر مدل‌های قبلی، یعنی «نسبت میانگین‌ها» بهمراه فاصله اطمینان ۹۵ درصد مربوطه، برآورد می‌گردد که همان شاخصی است که برای ارزیابی برابری در این شرایط، بدنبال آن هستیم. حال با استفاده از مزیت مدل رگرسیون خطی در شرایط ذکر شده که امکان وارد نمودن متغیرهای دیگر را نیز به ما می‌دهد، می‌توانیم متغیر سنجش پیامد اولیه در سیکل ۱ شیمی درمانی (بعنوان سنجش پایه)، البته در مقیاس لگاریتمی (چون این متغیر با متغیر پیامد اولیه در مقطع زمانی سیکل چهارم شیمی درمانی از نظر نرمال نبودن، مشترک است) را نیز وارد مدل رگرسیون خطی نموده و حال می‌توان با برآورد ضریب زاویه (ضریب بتا) متغیر گروه درمانی، این بار شاخص اندازه اثر «نسبت میانگین‌های تصحیح شده» یا Adjusted Mean Ratio، بهمراه فاصله اطمینان ۹۵ درصد مربوطه، برآورد نمود. لازم به ذکر است که در این رویکرد نیز برای ارزیابی تحلیل برابری با استفاده از این شاخص پیشگفت، مشابه مدل یا رویکرد C، آستانه یا مارژین برابری را از حداقل ۰.۹ تا حداکثر ۱.۱ در نظر گرفتیم.

✓ **مدل E- رویکرد استفاده از تفاضل میانگین‌ها با استفاده از میانگین هرس شده یکطرفه[5]:** این رویکرد، بعنوان یک رویکرد مبتنی بر «تحلیل حساسیت» بکار گرفته شده است. چنانچه عامل اصلی خارج شدن توزیع پیامد اولیه یا شمارش مطلق نوتروفیلی از تویع نرمال را، بدلیل اثرات شدید داده‌های پرت، بخصوص در جهت سمت راست یا جهت مقادیر بزرگتر یا مقادیر مثبت توزیع این متغیر بدانیم، می‌توانیم از یک راهکار نسبتاً ساده و قدیمی، تحت عنوان تولید «میانگین هرس شده» استفاده نمود[58]. در این رویکرد، درصدی از مقادیر، در یک یا دو سوی توزیع متغیر، حذف گردیده و مجدداً شاخص مرکزی میانگین محاسبه می‌شود. این مقدار از ۲.۵ درصد تا ۲۰ درصد متغیر است. اما از آنجا که حذف داده های پیامد اولیه در سوی مقادیر کمترین شمارش نوتروفیل‌ها، کاملاً نتایج را از اعتبار ساقط می‌نماید (بدلیل حذف یا مخفی شدن وضعیت عدم تاثیر دارو)، فلذا در این رویکرد، فقط از یک سوی این متغیر، مجموعاً ۵ درصد مقادیر ماکزیمم، بتنهایی حذف گردیده و مجدداً میانگین مربوطه، محاسبه گردید. در این شرایط به این شاخص مرکزی جدید، «میانگین هرس شده یکطرفه» می‌گویند. ضمناً برخی متخصصین آماری اعتقاد دارند که در داده‌هایی که از نظر توزیع، توزیع‌های با کشیدگی (چولگی) شدیداً مثبت یا راست[6] روبرو هستند، نیازی به حذف یا هرس متغیر در دو سوی توزیع نداشته و فقط می‌تواند در همان جهت مقادیر ماکزیمم (یعنی همان جهتی که داده های پرت موجب تاثیرات سوء بر روی متغیر گردیده است) حذف مقادیر انجام گیرد [60].

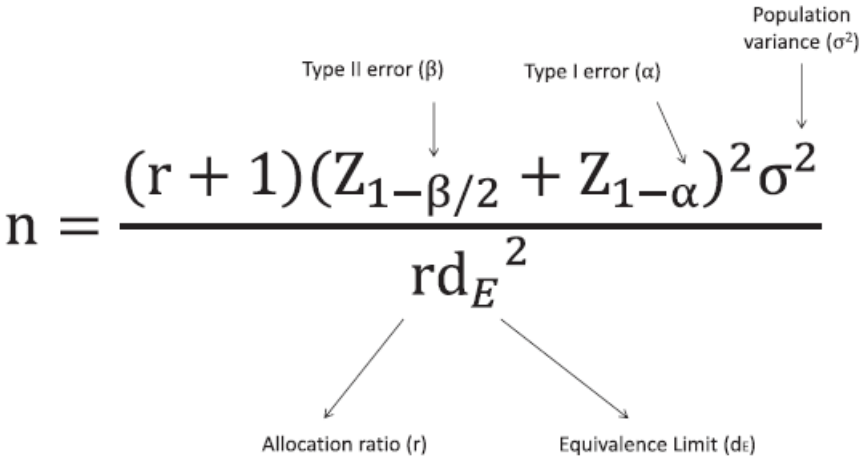
[5]One-sided Truncated Mean
[6]Highly Positive Skewed Data

- ✓ در این رویکرد (مدل E)، ابتدا برای پیامد اولیه، در دو مقطع زمانی سیکل ۱ و ۴ شیمی درمانی، با استفاده از توزیع آنها، ابتدا نقطه متناظر با صدک ۹۵ آنها مشخص گردید و سپس مقادیر بزرگتر از آن مقدار عددی، از تحلیل‌های آماری صورت گرفته در مدلهای E و F حذف گردیدند (توجه شود که فقط در این تحلیل‌ها از دیتای این مطالعه حذف شدند). این مقدار در پیامد شمارش مطلق نوترفیل‌ها در مقطع زمانی سیکل ۱ و سیکل ۴ بترتیب ۷۶۷۶ و ۱۰۸۰۰ بود. به این ترتیب در هر یک از این متغیرها، ۵ نفر واجد شرایط مذکور بودند که ۲ نفر از این افراد در دو وضعیت (هر دو متغیر سنجش پیامد در سیکل‌های ۱ و ۴) در این گروه قرار می‌گرفتند، فلذا مجموعاً از این تحلیل‌ها، ۸ نفر حذف شدند.

- ✓ **مدل F- رویکرد استفاده از تفاضل میانگین‌های تصحیح شده با استفاده از میانگین هرس شده یکطرفه:** این رویکرد نیز مشابه رویکردهای قبلی، شکل یا فرمت تصحیح شده، رویکرد قبلی می‌باشد. به عبارت دیگر در مدل E، با توجه به توصیه اکید متخصصین آمار و متدولوژیست‌های کارآزمایی‌ها، نیاز به تصحیح شاخص اندازه اثر مربوطه، با مقادیر سنجش پایه پیامد کمی مربوطه، وجود دارد. در اینجا نیز بمنظور سهولت انجام تحلیل‌های آماری و سهولت استخراج یافته ها، بخصوص فاصله اطمینان‌های مربوطه، از مدل رگرسیون خطی تک متغیره و چند متغیره (دو متغیر مستقل) استفاده گردید.

Sample size determination:

To calculate the sample size, the following formula and one of the papers [61] related to the calculation of the sample size were used in the clinical trials:



In this formula, "r" is the sample size ratio between the two arms or the clinical trial groups, and in the equal sample size this ratio is equal to 1. α and β are respectively the first and second type errors, which are commonly used in clinical trials, these two types of errors are recommended to be 5% and 10%, respectively. "d_E" The maximum acceptable clinical difference based on the primary outcome was to accept the equality between the two groups. In this trial, for the ANC variable, 200 neutrophils were considered. "σ^2 "is also the variance of the initial outcome, or neutrophils.

Changes in the implementation of the study and previous projections:

During the study and after several months from the onset of the illness, the work of the illness was slow and after visiting the organization and team of the Ethics Committee from the Shariati center and acknowledging the slow pace of the illness, with the consultation and approval of the principal facilitator of the project, Dr. Mousavi in Tehran, the cooperation of blood and oncology specialists in Rasool Akram and Firoozgar hospitals was also used. Therefore, by contracting with them, the rate of illness multiplied and within one month of the illness was completed.

At the beginning of the study, the number of patients was considered equally for each center, but due to lack of sufficient patient in Shiraz and Gorgan centers, the most patients were admitted by the center of Tehran. After the completion of the illness, complete CRFs were completed in all centers to check and confirm the delivery of Dr. Mousavi. Unfortunately, in one of the centers, despite the contract with one of his experts, he did not cooperate to introduce the patient. Therefore, with the help of the principal, they used one of the other doctors who did their best to work with the study team.

Finally, although initially with three physicians began in three study centers, but due to the slowdown in the rate of illness, which resulted in a loss of time and approaching the date of drug use and loss of funds, in the middle of the work with the coordinator, the number of physicians Our colleague was 14, who managed to accelerate the process of illness with careful scheduling and successive collaborations.

The increase in the time of illness, which should be completed in year 96, resulted in the completion of the time of study insurance and extended for the year 97 and the continuation of the sickness insurance plan.

تغییرات در اجرای مطالعه و پیش بینی های انجام گرفته قبلی:

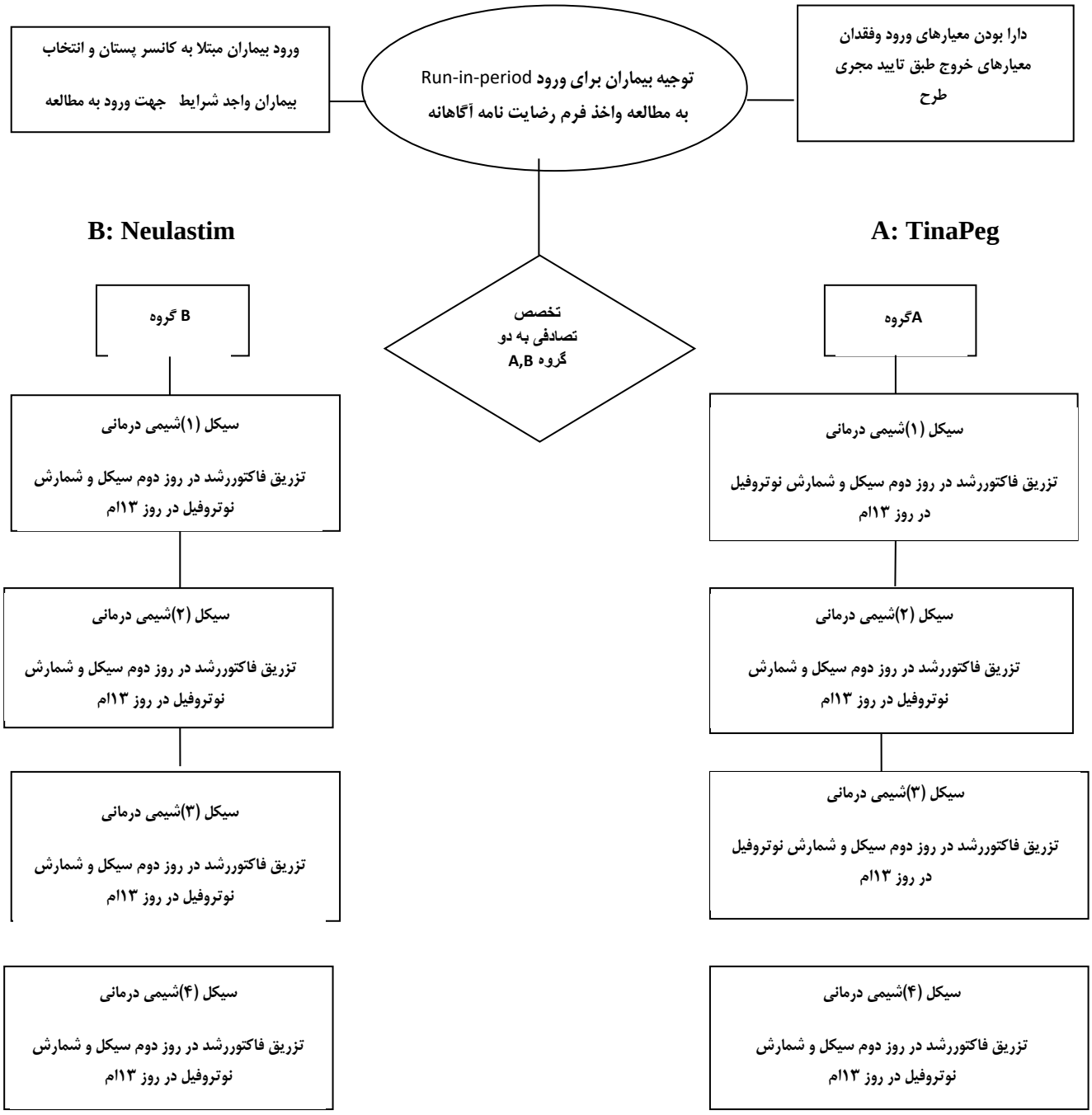
در حین انجام مطالعه و بعد از گذشت چند ماه از شروع بیمارگیری, کار بیمارگیری به کندی صورت می گرفت و بعد از بازدید سازمان و تیم کمیته اخلاق از مرکز شریعتی و اذعان به کندی سرعت بیمارگیری با مشورت و تایید مجری اصلی طرح جناب دکتر موسوی مقرر گردید در تهران از همکاری متخصصین خون و انکولوژی بیمارستان های رسول اکرم(ص) و فیروزگر نیز استفاده شود لذا با عقد قرارداد با آنان سرعت بیمارگیری چند برابر گردید و ظرف مدت یکماه بیمارگیری به پایان رسید.

در ابتدای مطالعه تعداد بیمار برای هر مرکز بطور مساوی در نظر گرفته شد ولی بعلت نداشتن بیمار کافی در مراکز شیراز و گرگان, بیشترین بیمار توسط مرکز تهران پذیرش گردید. بعد از اتمام بیمارگیری CRF های تکمیل شده در همه مراکز جهت بررسی و تایید تحویل آقای دکتر موسوی گردید. در یکی از مراکز متاسفانه علیرغم عقد قرارداد با یکی از متخصصین ایشان هیچگونه همکاری در جهت معرفی بیمار بعمل نیاورد لذا با کمک مجری اصلی از یکی دیگر از پزشکان استفاده شد که نهایت همکاری را با تیم مطالعه انجام دادند.

در نهایت با اینکه در ابتدا با سه پزشک در سه مرکز مطالعه آغاز شد ولی به همان دلیل کندی سرعت بیمارگیری که باعث از دست رفتن زمان و نزدیک شدن به تاریخ مصرف دارو و اتلاف بودجه می گردید لذا در اواسط کار با هماهنگی مجری محترم تعداد پزشکان همکار به ۱۴ نفر رسید که با برنامه ریزی دقیق و سرکشی های متوالی و همکاری جدی تر همکاران توانستم روند بیمارگیری را تسریع ببخشیم.

افزایش زمان بیمارگیری که باید در سال ۹۶ به اتمام می رسید منجر به اتمام زمان بیمه مطالعه گردید و برای سال ۹۷ و ادامه کار بیمارگیری بیمه نامه تمدید گردید.

فلوچارت شرکت کنندگان در مراحل مختلف مطالعه:



Deviation from the protocol:

Although in this trial, as well as many clinical trials, it is ideal that all eligible patients follow the protocol, but potentially there is a possibility of conditions that require a change in the patient / patient's treatment process:

A) One of the most probable deviations from the protocol in this trial was the change in pegilated granulocyte stimulus factor from the new invoiced condition (TinaPeg) to the standard factor (Neulastim) due to the occurrence of adverse / life-threatening complications / complications Leukocytosis and acute respiratory syndrome (ARDS) associated with this factor. In other words, the patient shifts from arm A to arm B in this situation (it should be noted that there was no severe and life-threatening adverse event in the Tina therapy prior to the clinical trial)

B) Another likely occurrence is the occurrence of adverse or life-threatening complications in the B arm, in which case the patient's therapist will inevitably discontinue the course of the growth factor or even terminate the patient's chemotherapy.

C) Another condition, the discontinuation of the patient's cooperation in each of the therapeutic arms and during the study period or any of the chemotherapy cycles, which can be caused by a variety of causes, such as a complication which is important and significant from the viewpoint of the patient. Migrating

a patient from the geographical area of the study area, which makes it difficult for her to travel, death, or any other reason.

In Situation A, both the Intention to treat and Per Protocol approaches will be used to analyze the data from the trial and the findings will be presented separately in the event of inconsistency or non-conflict. The reason for this is the evidence from a systematic review study comparing the two approaches sought in a large number of clinical trials conducted internationally (23). In situations, "B" and "C", which will result in missing data in the clinical data set, efforts will be made to ascertain as much as possible the data from the primary and secondary consequences of the last chemotherapy cycle of the patients in question. To be used for analysis. Meanwhile, analyzing the data by separating the quadruple cycles of the study and reporting them separately was an appropriate solution for these two situations.

How to randomize and blind the study

The method of randomization and blindness was done. First, using random numbers and random letters, a list was prepared and for each patient who had 4 injections, 1 and 2 letters were defined on the medicine box. Conformity boxes were prepared on which the generic drug name was registered, as well as non-marketable and exclusive trial terms. The boxes were completely shaped. Then the medications were removed from the original box and the same label as the drug code was written onto the original label that completely covered the material. Medications were placed in a refrigerator at a temperature of 2-8 ° C, and used to transfer to the centers from dry ice ionolite to maintain a cold chain transfer time. For all three

centers, the refrigerator company was purchased and delivered so that the place of preservation of drugs does not cause disturbance to the routine work of the centers, which usually lack the availability of such goods. The number for drugs was from 1 to 40 with 1, 2, 3, and 4, respectively, which included Tehran, Shiraz, Gorgan and Iran, and two Latin letters and one number that was considered the drug code. Prescription drug No. 1 was for the first patient. And number 2 for the second patient to the last number and the last patient. The code for the patient's CRF and the first letter of the patient's name was the patient identification code that was written.

research limitations:

The high costs of materials and facilities and a large number of samples have caused difficulty in conducting experiments, especially since it was very difficult to produce a similar drug at the start of the study. The very high sample size and follow-up treatment in four steps made it harder to work and progress the plan than the scheduling schedule. Also, due to changes in the preferred regimens in the NCCN guidelines in 2014, the TAC treatment regimen the preferred treatment for other post-surgical chemotherapy was changed, so in order to comply with the research protocol as well as the updated international cancer guidelines, the patients were selected to chemotherapy preferably before surgery, In this case, in addition to observing the research protocol, the patients are in accordance with the defined standards the treated. This inevitably led to a delay in the illness. Thus, 40% of the patients before surgery and 60% of them had undergone chemotherapy after the operation, although this was not related to the project and has no effect on the use of the drugs under study.

For all patients in all centers in the four stages of chemotherapy, the adriamycin diet with cyclophosphamide was used and, if necessary and according to the doctor's diagnosis, taxane was used after 4 stages of chemotherapy .

TIME FLOW

Visit No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Day	1	12±1	14±1	26±1	28±1	40±1	42±1	54±1
Activity	Screening /Treatment	visit	Treatment	visit	Treatment	visit	Treatment	visit
Consent	X							
History	X							
Pathology	X [a]							
Pathological and Clinical Staging [b]	X							
Drug dispensing	X		X		X		X	
Blood sample [c]	X	X	X	X	X	X	X	X
Whole body bone scan	X							
CT scan of Thorax and abdomen	X							
Concomitant Medication	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X

a) One pathological result is enough – the historic data will be used.
b) Size of tumor according to greatest diameter, Extension and Number of lesions (T stage), their location, presence of distant metastases, and regional lymphadenopathy.
c) Blood samples of screening day, days 1,12,14,26,28,40,42and 54 are used for safety (CBC)

ADVERSE EVENTS:

Toxicity / Grade	Grade4	Grade3	Grade2	Grade1	0
Platelet count/ml	Plt<10000☐	Plt<50000≤10000 ☐	Plt<75000≤50000☐	Plt<150000≤75000	NL ☐
Absolute neutrophil count	ANC <200 ☐	ANC 200- 500 ☐	ANC 500-1000 ☐	ANC 1000-1500☐	NLANC <1500 ☐
WBC	ANC <307 ☐	ANC 307- 769 ☐	ANC 769-1538 ☐	ANC 1538-2307 ☐	NLANC <2307 ☐
Hb	9<Hb ☐	9≥10>Hb ☐	10≥11>Hb ☐	11mg/dl≥12> Hb☐	NL ☐
Bleeding	Transfusion needed ☐	Sever bleeding ☐	Moderate bleeding ☐	Mild bleeding☐	None ☐
Fever	T>40 more than 24h ☐	T>40 less than 24h ☐	39.1-40c ☐	38-39c☐	None ☐
Nausea	Very sever ☐	Sever ☐	Moderate ☐	Mild ☐	None ☐
Vomiting	Hemodynamic collapse ☐	6 episode ☐	2-5 episode in 24h ☐	1 episode in 24h ☐	None ☐
Diarrhea	Hemodynamic collapse ☐	More than 7 episodes ☐	4-6 episode a day ☐	Less than 4 ☐	None ☐
Bone pain	Not Controlled with NSAIDs ☐	Recurrent ☐	Controlled with NSAIDs ☐	Mild ☐	None ☐
Myalgia	Not contorted with NSAID ☐	Recurrent ☐	Controlled with NSAIDs ☐	Mild ☐	None ☐

Special considerations for multicentre studies reports:

This study was conducted in three centers including Shariati Hospitals, Rasool Akram and Firoozgar in Tehran and Namazi Shiraz and 5 Azar Gorgan hospitals in cooperation with 14 doctors and 6 nurses. Coordination between these centers and the delivery of drugs and related forms with respect to the dimension of the distance and frequent visits and the elimination of their deficiencies despite the difficulty of working happily, with the least difficult.

Findings:

Table 1) Distribution of demographic variables and other important variables in the baseline phase (before intervention) in patients divided into two groups of treatment

متغیر	TinaPeg (n=51)	Neulsatim (n=51)	P value
سن mean (sd)	۴۵.۶ (۱۰.۷)	۴۸.۱ (۱۰.۸)	۰.۲۴
وزن mean (sd)	۷۱.۴ (۱۴.۸)	۷۱.۹ (۱۱.۸)	۰.۸۳
مرحله (Staging) سرطان پستان:			۰.۶۷
Stage 1no (%)	۱ (۲.۰)	۲ (۳.۹)	
Stage 2no (%)	۲۴ (۴۷.۰)	۲۷ (۵۲.۹)	
Stage 3no (%)	۲۵ (۴۹.۰)	۲۰ (۳۹.۳)	
Stage 4no (%)	۱ (۲.۰)	۲ (۳.۹)	
شهر مرکز مطالعه (بیمارستان):			۰.۶۴
تهران (بیمارستان های تهران) no (%)	۳۴ (۶۶.۷)	۳۰ (۵۸.۸)	
شیراز (بیمارستان نمازی) no (%)	۶ (۱۱.۸)	۹ (۱۷.۷)	
گرگان (بیمارستان ۵ آذر) no (%)	۱۱ (۲۱.۵)	۱۲ (۲۳.۵)	

Table 2: Distribution of different outcomes of the trial in the basal phase, divided into two groups of treatment, with a significant difference between the two groups

P value	Neulastim Mean (sd) Median [P_{25}-P_{75}]	TinaPeg Mean (sd) Median [P_{25}-P_{75}]	پیامدها
۰.۱۷	۳۸۷۱ (۱۷۶۵) ۳۵۰۰ [۵۰۳۷-۲۷۴۰]	۴۲۲۳ (۱۵۱۲) ۴۱۴۰ [۴۹۶۸-۳۱۰۰]	شمارش مطلق نوتروفیلها
۰.۴۲	۶۹۲۶ (۲۵۹۹) ۶۶۰۰ [۸۷۰۰-۵۱۰۰]	۷۰۶۳ (۱۷۷۶) ۶۸۰۰ [۸۶۰۰-۵۸۲۰]	شمارش گلبولهای سفید
❋۰.۰۴	۱۲.۷ (۱.۳) ۱۲.۹ [۱۳.۶-۱۱.۸]	۱۲.۲ (۱.۱) ۱۲.۳ [۱۳.۰-۱۱.۶]	هموگلوبین
۰.۷۰	۲۷۷،۳۵۹ (۹۲،۶۲۷) [۳۱۲،۰۰۰-۲۲۲،۰۰۰] ۲۶۵،۰۰۰	۲۶۳،۰۳۹ (۸۲،۴۲۶) [۳۳۵،۰۰۰-۱۹۳،۰۰۰] ۲۵۶،۰۰۰	شمارش پلاکت

* Based on independent t test. The remaining p values are calculated based on the Mann-Whitney test (due to the lack of normal distribution in these variables).

Table 3 Summary of equivalence assessment findings with related indicators and size of power effects relation to the separation of the 6 models or approaches used

مدل یا رویکرد	نوع شاخص ارزیابی برابری	مقدار اندازه برابری (95% CI)	P value	نوع شاخص اندازه قدرت رابطه	مقدار اندازه قدرت رابطه (95% CI)
مدل A	تفاضل میانگینها	۱۱۹.۳ (-۱۱۶۲.۳ ؛ ۱۴۰۰.۸)	۰.۸۵	ضریب بتای استاندارد شده	۰.۰۱۹ (-۰.۱۷۸ ؛ ۰.۲۱۵)
مدل B	تفاضل میانگینها	-۱۶۰.۰ (-۱۳۴۷.۷ ؛ ۱۰۲۸.۱)	۰.۷۹	ضریب بتای استاندارد شده	-۰.۰۲۵ (-۰.۲۰۷ ؛ ۰.۱۵۷)
مدل C	نسبت میانگینها	۱.۰۶۲ (۰.۸۵۵ ؛ ۱.۳۲۰)	۰.۵۸	ضریب بتای استاندارد شده	۰.۰۵۵ (-۰.۱۴۱ ؛ ۰.۲۵۱)
مدل D	نسبت میانگینها	۱.۰۰۸ (۰.۸۱۷ ؛ ۱.۲۴۴)	۰.۹۴	ضریب بتای استاندارد شده	۰.۰۰۷ (-۰.۱۸۲ ؛ ۰.۱۹۶)
مدل E	تفاضل میانگینها	۴۳۵.۰ (-۴۱۲.۴ ؛ ۱۲۸۲.۵)	۰.۳۱	ضریب بتای استاندارد شده	۰.۱۰۶ (-۰.۰۹۹ ؛ ۰.۳۱۰)
مدل F	تفاضل میانگینها	۳۰۴.۴ (-۵۳۰.۳ ؛ ۱۱۳۹.۲)	۰.۴۷	ضریب بتای استاندارد شده	۰.۰۷۴ (-۰.۱۲۷ ؛ ۰.۲۷۵)

Table 4: Comparison of the contribution of mild neutropenia to the two groups of treatment and four chemotherapy cycles together with the relative risk index of this outcome

سیکلهای شیمی درمانی	TinaPeg n (%) (n=51)	Neulsastim n (%) (n=51)	Risk Ratio (95% CI)	P value
سیکل ۱	۱ (۲.۰)	۳ (۵.۹)	۰.۳۳ (۰.۰۴-۲.۷۸)	۰.۳۱
سیکل ۲	۲ (۴.۰)	۱ (۲.۰)	۲.۰ (۰.۲۰-۲۰.۵۵)	۰.۵۶
سیکل ۳	۳ (۵.۹)	۲ (۴.۰)	۱.۵۰ (۰.۲۶-۸.۵۶)	۰.۶۵
سیکل ۴	۱ (۲.۰)	۳ (۵.۹)	۰.۳۳ (۰.۰۴-۲.۷۸)	۰.۳۱
در هر سیکلی	۴ (۷.۸)	۸ (۱۵.۶)	۰.۵۰ (۰.۱۷-۱.۵۲)	۰.۲۲

❊Based on independent t test. The remaining p values are calculated based on the Mann-Whitney test (due to the lack of normal distribution in these variables).

Demographic characteristics and other basic characteristics of the participants in the study:

After the end of the trial, a total of 102 people entered the study and completed all the expected stages. The demographic and important characteristics and characteristics of these patients are summarized in two groups of treatment in Table 1. It should be noted that in all patients under study, women with breast cancer were in stages or stages one to four. As shown in Table 1, there were no significant differences between age, weight, and disease stages in two groups ($p \geq 0.24$). Approximately two thirds of the patients under

study in the center of Tehran (Shariati Hospital, Rasool Akram and Firouzgar) with 64 (62.8%), 23 (22.6%) patients were in the center of Gorgan (5th Azar Hospital) and the remaining 15 (14.6%) patients. In the center of Shiraz (Namazi Hospital), the treatment and study were not distributed and the distribution of patients in different centers did not show significant difference between the two treatment groups (p = 0.64).

Distribution of the initial outcome of this trial (neutrophil counts) as well as other blood markers (white blood cell count, platelet counts, and hemoglobin count) between the two treatment groups in the first chemotherapy cycle (day The thirteenth of the first cycle is shown in Table 2. It should be noted that the distribution of absolute neutrophil count, white blood cell count and platelet counts per milliliter of cubic blood were not distributed in normal groups and only the hemoglobin variable (in grams per deciliter) in two groups Distribution was normal. Therefore, in Table 2, for each of the four variables or important consequences, both the central and intermediate indexes as well as both the standard deviation index and the interval between the quartiles (the distance between the 25th and 75th percentiles, or the first and third quartiles), It has been reported that the distribution status of these variables in the two groups is more specific. Also, to compare the distribution of these variables, in the two groups, only the hemoglobin variable (due to the normal distribution of this variable in the two groups), independent t-test for two groups and for other variables (due to the lack of normal distribution), and the nonparametric test ,Mann Whitney, was used.

The absolute neutrophil count in the Tinapag group was 4223 (per cubic millimeter) and in the neulastim group was 3871 (per millimeter cubic meter). Therefore, the average absolute count of neutrophils in the Tinapag group is greater than 350 neulastim, although this difference was not statistically significant (p = 0.17).

Comparing the distribution of other cells or blood markers between the two groups, only the distribution of hemoglobin was significant between the two groups (p=0.04).

Evaluating the equality of the treatments, based on the initial outcome:

The mean changes in the initial outcome of this trial (absolute count of neutrophils) at four times (on the thirteenth day of the first to fourth cycle chemotherapy cycles) are shown in Fig. 2. This graph shows a gradual increase in the mean increase in the absolute count of neutrophil counts in the two treatment groups, and after approximately four cycles of chemotherapy, in the two therapies of tinapeg and neulastim, an increase of 26 and 34%, respectively, was observed in these blood cells. In the fourth cycle (the final measure of the initial outcome in this trial), the mean neutrophil counts in the two therapies of tinapeg and neulastim were 5315 and 5195 (in millimeters of cubic blood), and the mean difference of these cells was about 120. This difference was not statistically significant ($p = 0.82$). Meanwhile, the difference in the mean neutrophil count in the two treatment groups, at the end of the fourth cycle, was about one third of the difference between the mean numbers of neutrophils in the two treatment groups, in the first cycle of chemotherapy with the two drugs studied.

However, due to the multidisciplinary nature of the trial, although the sample size of the patients under study in different cities (hospital centers in three cities of Tehran, Shiraz and Gorgan) was not the same, however, considering the importance of evaluating the outcomes of the study, divided into all centers, Changes in the mean absolute neutrophil count in the four cycles of chemotherapy in the three cities are shown in Figures 3.5. Fortunately, the pattern observed in the center of Tehran (Shariati Hospital, Rasool Akram Say and Firouzgar Tehran), the highest proportion of patients in this center, was similar to the observed pattern of patients, but this pattern was observed in two cities of Shiraz and Gorgan, The difference was that in view of the small sample size in these two centers and the increase in random error, these observed patterns are inevitable.

Equality analysis with respect to margin or threshold defined as "prior" or priori:

The outcome of the evaluation of the equivalence of the two types of treatment used in this trial, based on the models or approaches explained (Models A to F described in the statistical analysis of the method of work) are:

As described in the above six-model models or approaches, in these models, two types of size or index were used to compare the outcome of the trial from an equality perspective based on the initial outcome distribution (absolute neutrophil count): one the median averaging index is compared with the number 200 according to the threshold or margin defined in the proposal for this trial. But the other size is the average ratio index, which in two models of the six models analyzed, their output is formed and unfortunately for this index, as in the previous index, threshold or margin is not defined.

Of course, it should be noted that, as the zero point in the averages difference indexes indicates a non-difference in the outcome or result of the two groups (or several groups), in the average ratio indices, the same number shows the previous result. However, the need for a threshold for decision-making trials, especially in equivalence or non-inferiority trials, is an inevitable necessity (see Figure 2). In other words, as the decision-making index is the difference in averages, determining the threshold of 200 neutrophils indicates that if the two confidence limits of this decision-making index are within the distance or range of -200 to +200, Then the equivalence hypothesis is acceptable for the two interventions under study (each of the scenarios c, d, or e) and otherwise it can not be accepted.

The results, based on the difference between the means is shown in Figure 6. As mentioned in the description of the analyzed models or approaches, out of six models, four approaches have the output of the "difference of means" indicator. In the two models A and B, the point

difference average index was calculated to be 119.3 and 160.0, respectively. Although these two points are within the range of the threshold or margin (ie, from at least -200 to +200), but if these two models are considered, these ranges are very wide And includes an interval of at least 2300 nouns (with a primary outcome measurement unit, the absolute neutrophil count), which is close to 6 times the range or threshold of equality. Obviously, one of the main reasons for the widespread reliability of this range is high. The dispersion index (standard deviation or variance) is the absolute neutrofil count variable. However, the conclusion based on these two analytical models should be considered "non-deterministic", although the "equivalence" can not be ruled out due to the point average estimates of the two approaches.

The E and F models can be considered similar to the corresponding models A and B, because according to the method of eliminating the percentage of distraction data and recalculating the central mean of the index, one of the methods that has long been considered by the statisticians Has been located. Meanwhile, since the removal of the minimal values of the outcome of the absolute neutrophil count, can lead to an over-estimation of the mean bias, then the deletion or pruning of the data values is limited only to the maximum values. The remaining steps of calculating or estimating the decision-making index of these two models, the "difference of means", are similar to those of the two previous models, and the result is also shown in Fig. In these two models, the median difference in spot estimation was not within the range and in contrast, it is in the range of the superiority of TinaPeg treatment compared to Neulastim treatment. At the same time, due to the relative reduction of the dispersion index (due to a 5% decrease in the amount of distortion), the total 95% confidence interval of the average difference in these two models was about 30% lower than the previous models (models A and B) showed. But in terms of the outcome of these two models, it should be acknowledged that by limiting the confidence intervals of the decision-making index, the

final result does not lead to an interpretation of the superiority or superiority of the aforementioned treatments, and even with these results, A repeat case with higher sample volumes, or a secondary combination of multiple initial studies with this goal (ie, systematic review and meta-analysis), can also result in a credible equivalence. But this analysis shows that it is very unlikely and unlikely that the final conclusion or inferiority of the inferiority (that is, the effectiveness of TinaPeg is weaker than Neulastim), which can reasonably be considered important for policy makers of the country, can be very significant.

In addition to the four approaches or model analyzed, two other models, under the headings of the C and D models, used another decision-making indicator. In other words, in these two approaches, instead of solving the problem of leaving the distribution of the main consequence of the normal distribution, with the help of eliminating data on the maximum distribution of this distribution, a well-known, agreed, and valid variable change was used. Fortunately, the theoretical logic behind this approach is growing, and besides, the conditions for the use of single-variable and multivariate analyzes are also quite feasible and logical. For example, the use of parametric analysis of linear regression is allowed in these conditions, and even fortunately the relevant index has the ability to compare between two single-variable and multivariate conditions. The only difference that should be considered in comparison between these two models or approaches with previous models is the type or nature of the decision index that changes from the "averages difference" to the "average ratios" indicator. Find out obviously, the neutral or null value of this index, which is equal to 1, should be considered in comparison with the null value of the "Mean difference" indices, which is a numerical value of zero. Perhaps, in order to understand the comparisons of these two indicators, comparing the features of the "risk differential" indicator with the "relative risk" or relative risk is much closer to this comparison. Perhaps the only challenge or

limitation of using this index (the ratio of averages) in this trial is the lack of clarity of the threshold of equality with the "prior" or priori approach, but, nevertheless, according to the explanations explained in the two models C and D, The threshold is expected to range from 0.9 to 1.1. As shown in Fig. 7, the spot estimation of the "average ratio" indices in the two models C and D is equal to the range or margin, but the lower and upper bounds of the 95% confidence interval indicators that are the product of two linear regression models (once a single-variable model and one-time model in the bivariate model corrected for the absolute logarithm of the neutrophilic number in the first cycle of chemotherapy) are beyond the threshold of the margin. Which is similar to the situation in the two previous models. However, the point estimate of the averages ratio in these two models is more than 1, which means that the central index of the absolute number of neutrophils in the TinaPeg group is slightly higher than the central index of absolute neutrophil counts is Neulastim group.

As we all know, in all the guides for writing essays in general, as well as the printed guides of articles in clinical trials specifically (at the top of their guide to writing articles CONSORT, the last edition of which, CONSORT-2010), it is emphasized that it is necessary to the report of the hypothesis testing approach, which is in fact the same as the report of p value, is to be reported as "effect size" in accordance with the statistical test used. Therefore, because of the six-model used in the statistical analysis of this trial, the linear regression model is used, so it is necessary to measure the index of the effect's magnitude (or relationship's power) of this model, the index of "corrected beta coefficient" To be reported. In Fig. 8, the results of the point and distance estimation (95% confidence interval) of this index are reported separately from the six models mentioned above. Fortunately, the distribution of this power index of relationship in six analytical models shows the consistency of the results with previous analyzes and all the analyzed models indicate that the two

interventions did not differ (or equalize the effects), while in most models, if we want to estimate The point of these indices is also to decide that it is possible to claim that Tina_PEG's intervention against Neulastim is relatively weak. Because the estimate of the point of this magnitude, in the six analytical models, fluctuated from its weakest, 0.01 to the strongest, ie, 0.11. Since Professor Jacob Cohen, in his valuable book on applied regression, estimates that the standardized beta coefficient between 0.05 and 0.10 is inadequate for decision change (policy-making or performance) [62], it can be deduced that in the strongest estimate of this effect size, there is no difference in practice between the two therapeutic interventions. It should be noted that all the analyzed indices in six models or approaches, by the type of relevant index as well as the level of p value obtained are summarized in Table 3.

Analysis of data based on secondary outcomes:

There were no moderate and severe neutropenia in all of the patients with the desired treatment, and only mild neutropenia (absolute neutrophil counts between 1000 and 1500) was observed in some patients in each of the four treatment cycles. Table 4 shows the comparison of the proportion of patients with this degree of neutropenia, along with the relative risk index of this outcome. A total of 12 patients in two treatment groups were subjected to mild neutropenic group in at least one of four periods of neutrophil counts. 4 patient were in the TinaPeg group and 8 in the Neulastim group. However, the analysis of these data showed that the risk of this complication in patients treated with TinaPeg was 50% lower than that of Neulastim treated patients, but this difference was not statistically significant.

Bone pain was observed in 8 patients in both groups. Five of these patients were in the Neulastim group and three in the TinaPeg group. This difference was not statistically significant ($p = 0.46$) and the risk of this complication in the patient treated with TinaPeg was

40% lower than the patients treated with Neulastim (relative risk: 0.60 and confidence interval 95 %: 2.35-0.15). However, in the severity of bone pain between the two groups, severe, moderate and mild bone pain was observed in the Neulastim group, respectively, in 1, 1 and 3 subjects. There was no severe bone pain in the TinaPeg group and the incidence of mild to moderate pain was reported as 1 and 2, respectively.

Other data analyzed:

Diagrams 9-11 show the distribution of white blood cells, hemoglobin and platelet count in four chemotherapy cycles, divided into two groups.

The mean white blood cell count in the first chemotherapy cycle in both TinaPeg and Neulastim groups was 7063 and 6926, respectively, which did not differ statistically between them ($p > 0.05$), however, these values after the fourth cycle of chemotherapy and at the end of trial also increased by approximately 10% in both groups to 7791 and 7636, respectively, which did not show statistically significant differences at this time ($p > 0.05$).

The mean hemoglobin of the TinaPeg group from the Neulastim group was lower than 0.5 g / dl in the first cycle of chemotherapy (12.2 versus 12.7), and this difference was statistically significant (Table 2). Chart 10 shows the progression of mean hemoglobin changes in the two treatment groups, until the fourth or final study, the mean of hemoglobin in the two groups decreased to 1.2 ± 11.5 and 1.5 ± 11.8, respectively (decrease by about 7-6%), However, the difference in hemoglobin levels at the end of the study or in the fourth cycle of chemotherapy was not significant ($p = 0.23$).

However, the average platelet count in the first cycle of chemotherapy was less in the TinaPeg group than in the Neulastim group (about 263,000 versus 277,000), but there was no significant difference between the two treatment groups (Table 2). During the next chemotherapy cycles, the relative advantage of platelet count in the Neulastim group was similar to that of the primary model, and eventually in the fourth cycle or the end of the study, respectively, in these two groups was approximately 261,000 and 305,000, which is statistically significant Was significant ($p = 0.05$).

Also, in Chart 12, changes in neutrophil counts absolute distribution (as the primary outcome) in the four cycles of chemotherapy after withdrawal of 5% of the maximum values and the estimated median pruned one-sidedness are observed.

Measuring adherence to treatment by subjects:

In this trial, an indicator for completing the treatment according to the four chemotherapy cycles (along with the injection of medications) was used to assess the adherence to treatment in patients. In other words, if a patient is defined in accordance with the planned program, as defined in the methodology of this trial project, he will refer to the prescribed date for his or her desired medication and also to test for pareclinical tests for his markers or blood cells. Related to each quadruple cycle, known as "adherence to therapy", and vice versa, if at least in a chemotherapy cycle, does not appear at due time, or for whatever reason, the injection of the drug in question is not "non-adherent" "It is defined as treatment. Fortunately, according to the findings of this study, all patients in the study group had 100% adherence to treatment in two treatment groups and in all of the hospitals.

Final discussion and conclusion:

Based on the nature of the hypothesis of this trial, which is of the type and based on the distribution of the initial outcome in this trial, we tried to analyze the paradigms from this perspective from different perspectives and approaches (six models or approaches A to F). The summary of these analyzes can be classified into two parts. In the first section, where all analyzes were judged based on data collected or actual data, namely, models A, B, C and D, two of the "difference in averages" and "ratio" Averages were used for this analysis. The result of these four approaches was common in these two characteristics (Figures 6 and 7):

1- Point estimates of decision indices (both indicators) were defined in the region or threshold of equality.

2. The lower and upper bounds of these two indicators are located in each of the four models or approaches on either side of the threshold or margin (-Δ, + Δ). However, the widespreadness of this range in the mean difference index is higher than the averages ratio index, which can be attributed to the wider range of averages of the differential index, due to the extent of the absolute neutrophil counts variable, versus the averages ratio index , is more like relative indicators, the more limited its range of dispersion.

If we put these two characteristics together, according to analyzes of equality workings based on decision thresholds, it can be stated that perhaps the only challenge to proof of equality in this trial is the challenge of the low power of this analysis be statistical.

Two models of E and F can be interpreted as models based on sensitivity analysis. Because if the effect of elongation or skewness of the initial outcome that results in the exit from the normal distribution, as well as a significant increase in the variance or standard deviation of this variable, is to be interpreted from the perspective of the effect of subjugation on the size of the decision making principle in this study, then any logic-based approach A science

capable of reporting and comparing the main findings of the trial in two states of the existence of its causative causation and subjectivity without having to subjugate or at least minimizing the effect of this kind of subjugation is an approach based on "sensitivity analysis" and the recommendation of many trial methodologists is that at the time of writing the report In the final trials or articles, the sensitivity analysis approach is also needed in the form of a "follow-up analysis" or "secondary analysis".

Recently, in a review article, nine key questions related to the findings of a clinical trial that researchers (authors) need to evaluate and criticize the main result of the trial with these nine questions, and if at least one of these nine cases it is possible to influence the results; it should answer that question / question through a comparative approach. If this comparative approach shows that the presence and absence of a factor influencing subversion does not have a significant impact on the findings, then even the results of the trial could be referred to as "sustained". One of these nine questions is the question of the effect of overflow data or an abnormal distribution of outcome on the main results. Therefore, with this view, analytical models E and F can be considered as two perspectives based on the "sensitivity analysis" in this trial.

Now, if we interpret and conclude these two recent models on the basis of the above approach, we can extract two rather distinct interpretations, summarizing it as follows:

A) The distribution of the mean difference index, with the assumption that all or part of the causative agent causing the skewness or unpredictability of the data is resolved, is progressing towards the "superiority" of TinaPeg's treatment of Neulastim's treatment.

B. Given the widespread 95% confidence interval of the averages, we still can not see the result of equivalence as unlikely.

Made It can be concluded that if the main result obtained from the previous models is to be influenced by the anomalous distribution of the primary outcome, other than the result of equilibrium, this result with a high degree of certainty, the superiority of treatment Neulastim compared to TinaPeg treatment will not be. However, the results obtained from the sensitivity analysis pathway also emphasize the statistical power calculation.

To test the power of the statistical tests performed in the models or approaches, the SSI application of Stata 13 was used. This command is designed to calculate the sample size or power in parallel trials with hypotheses of superiority, equality, and non-inferiority. (Scenarios E and F), for a total of 2 different situations, the statistical power was calculated.

As predicted, the statistical power for the situation in accordance with scenarios A and B (conditions precisely the status of the data reported in this exercise) is about 4% and for the state of compliance with scenarios E and F (deletion of 5% of the data Perth peak of neutrophil counts) is about 7%. Calculating the statistical power of the statistical tests shows that if these data are the basis for the decision to design a trial study with the hypothesis, the sample size required is much higher than the present study and even the conditions that can be applied to it (With the SSI command, this sample size is about 1900 people per group or a total of 3800).

In this trial, none of the three scenarios or the predicted status of the protocol in the study did not show any deviation from the protocol, nor was any loss or loss of subjects (patients treated in treatment groups). Therefore, in practice, two strategies or strategies for analyzing the Intention to Treat (ITT) and Per-Protocol (PP) were not the same and resulted in a precisely single result. This can be considered as one of the positive points and advantages for this work. This finding can be attributed primarily to the richer experience of the company (Aria Tienagen Company) in relation to previous studies of the company and the exploitation

of previous lessons learned, as well as the product of the use of scientific solutions by managers and staff of the complex. .

From the limitations of this trial, there are two main constraints: the first important limitation is the very low power of this work, which, according to secondary analyzes, measures the power and its possible factors, as well as analyzes of sensitivities In fact, it can be concluded that the two treatments are equally acceptable. Of course, in designing alternative solutions / alternatives, the optimal or ideal power (ie, designing and implementing a trial with a much larger sample size than the current one) is to notice a lot of practical and budget differences that may move towards These alternative solutions in practice have encountered many problems.

Demographic characteristics and other basic characteristics of the participants in the study:

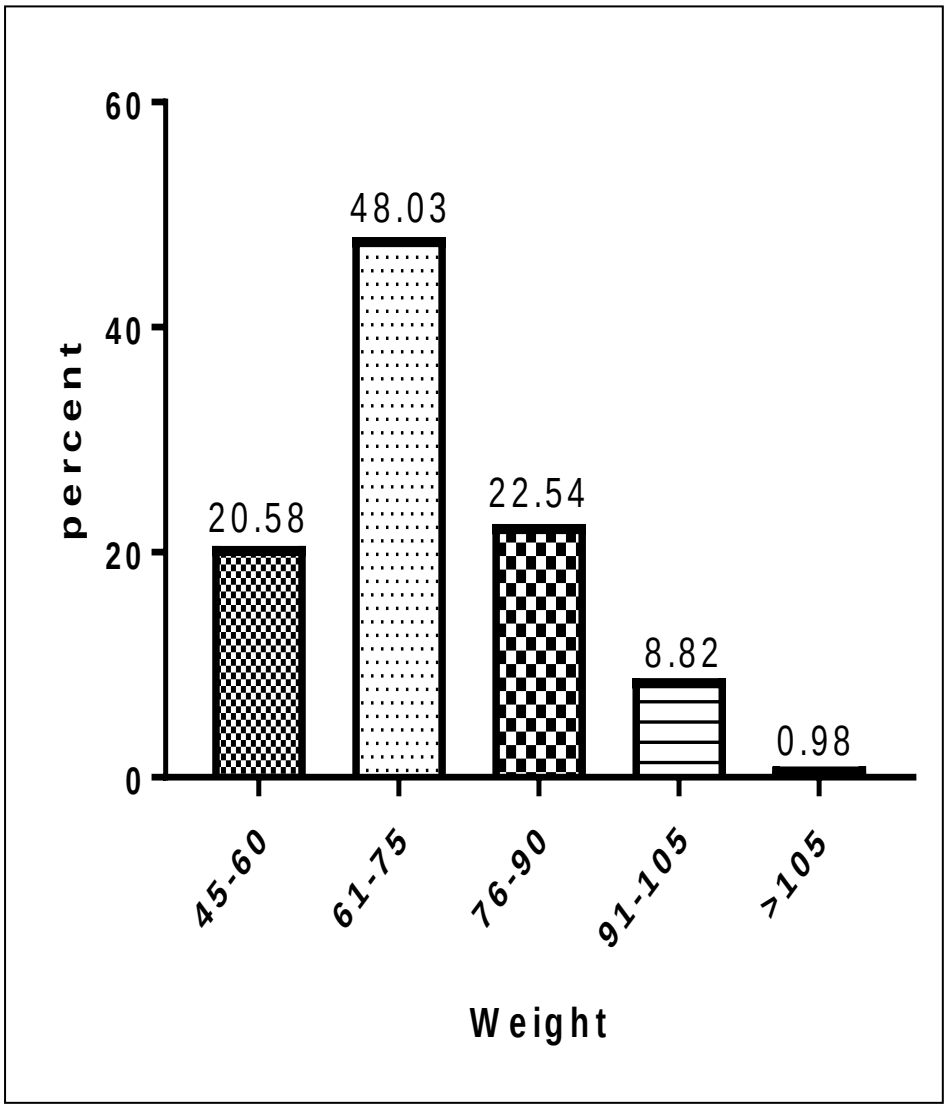
	Neulastim	TinaPeg

تعداد کل بیماران	۵۱	۵۱
تعداد بیماران مرکز تهران	۳۲	۳۲
تعداد بیماران مرکز شیراز	۸	۷
تعداد بیماران مرکز گرگان	۱۱	۱۲
Stage		
I	۲	۱
II	۲۷	۲۴
II	۲۰	۲۵
IV	۲	۱
سن		
۳۰-۲۰	۳	۳
۴۰-۳۱	۸	۱۳
۵۰-۴۱	۱۸	۲۰
۶۰-۵۱	۱۴	۹
۷۰-۶۱	۸	۶
وزن (کیلوگرم)		
۶۰-۴۵	۱۰	۱۱
۷۵-۶۱	۲۳	۲۶
۹۰-۷۶	۱۴	۸
۱۰۵-۹۱	۴	۵
۱۰۵<	۰	۱

بخش جداول, نمودارها و تصاویر:

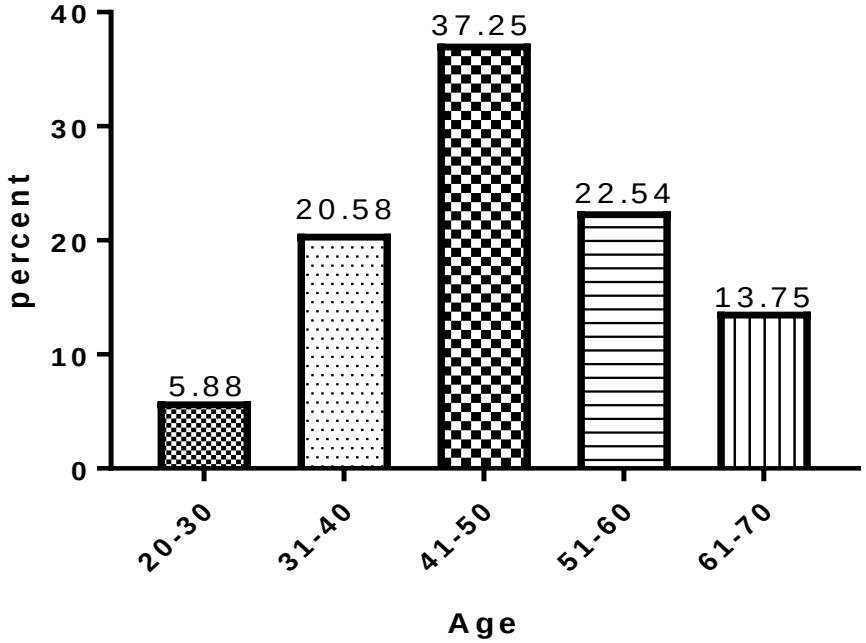
نمایش گرافیکی اطلاعات فردی:

نمودار و جدول توزیع وزن بیماران در مطالعه



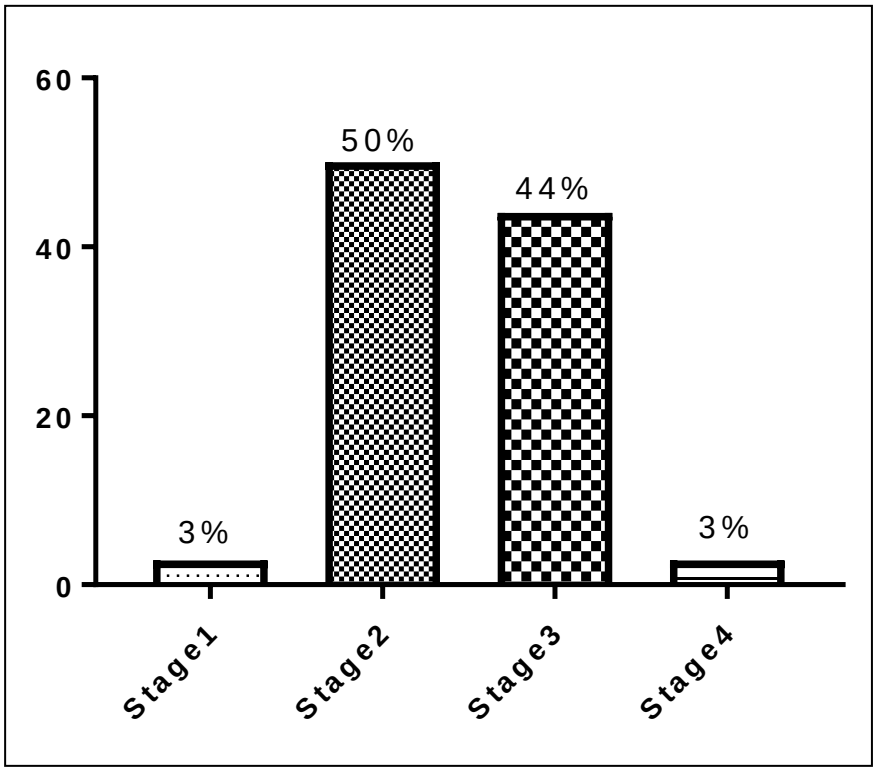
محدوده وزنی	۶۰-۴۵	۷۵-۶۱	۹۰-۷۶	۱۰۵-۹۱	۱۰۵<
تعداد بیماران	۲۱	۴۹	۲۲	۹	۱
درصد	۲۰/۵۸	۴۸/۰۳	۲۲/۵۴	۸/۸۲	۰/۹۸

نمودار و جدول توزیع سن بیماران در مطالعه



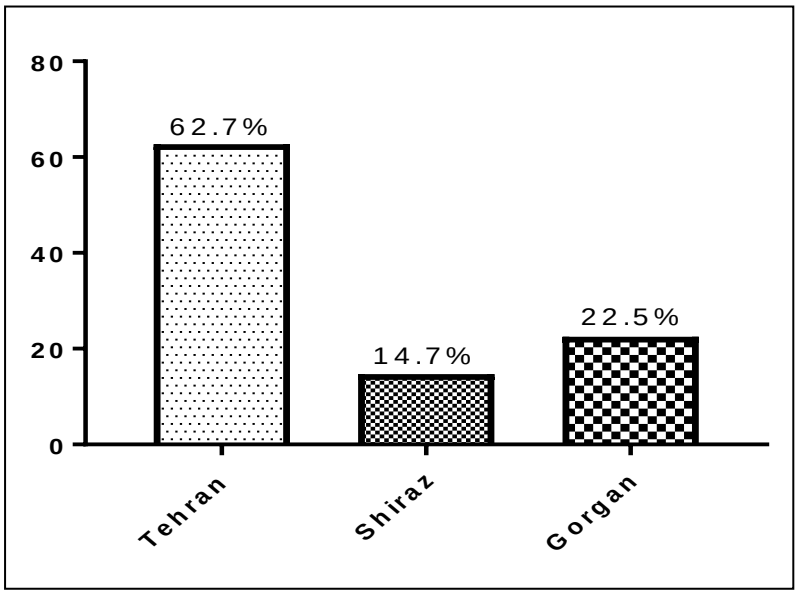
محدوده سنی	۳۰-۲۰	۴۰-۳۱	۵۰-۴۱	۶۰-۵۱	۷۰-۶۱
تعداد بیماران	۶	۲۱	۳۸	۲۳	۱۴
درصد	۵/۸۸	۲۰/۵۸	۳۷/۲۵	۲۲/۵۴	۱۳/۷۵

نمودار و جدول توزیع Stage بیماران شرکت کننده در مطالعه



شدت بیماری	Stage1	Stage2	Stage3	Stage4
تعداد بیماران	۳	۵۱	۴۵	۳
درصد	۲.۹	۵۰	۴۴	۲/۹

نمودار و جدول توزیع بیماران در مراکز مختلف مطالعه



نام شهر	تهران	شیراز	گرگان
تعداد بیمار	۶۴	۱۵	۲۳
درصد بیمار	۶۲/۷	۱۴/۷	۲۲/۵

جدول مقایسه عوارض نامطلوب داروهای مورد مطالعه در بیماران موجود در مداخله

Myalgia	Bone pain			Diarrhea	Vomiting	Nausea	Fever	Bleeding	Neutropenia*			Adverse events / Drugs
	G1	G2	G3						L	M	S	
0	2	1	0	0	0	0	0	0	4	0	0	TinaPeg
0	3	1	1	0	0	0	0	0	8	0	0	Neulastim

*سطح بندی شدت عارضه نوتروپنی در بیماران . L: ANC 1000-1500، M: ANC 500-1000 و S: ANC <200

نتیجه تحلیل برابری، براساس شاخص تفاضل میانگین‌ها و فاصله اطمینان ۹۵ درصد آن برای پیامد اولیه شمارش مطلق نوتروفیل‌ها در مقاطع زمانی سیکل‌های اول، دوم، سوم و چهارم:

سیکل‌های شیمی درمانی	TinaPeg n (%) (n=51)	Neulastim n (%) (n=51)	Mean Difference (95% CI)	P value
سیکل ۱	4223.03 (1512.0)	3886.6 (1806.4)	336.4	0.11
سیکل ۲	4861.4 (3386.0)	4852.6 (2274.7)	8.8 (-1124.4, 1142.0)	0.99
سیکل ۳	5179.5 (3334.4)	4777.4 (2149.8)	402.1 (-700.1, 1504.2)	0.47
سیکل ۴	5314.6 (3076.2)	5195.3 (3437.7)	119.3 (-1162.3, 1400.8)	0.85

مقادیر عددی در ستونهای مربوط به گروههای درمانی، بصورت mean (sd) می‌باشد.

مقدار عددی شاخص Mean Difference و علامت مثبت یا منفی این شاخص از فرمول $\mathbf{Mean_{TinaPeg} - Mean_{Neulastim}}$ بدست آمده است.

نتیجه تحلیل برابری، براساس شاخص تفاضل میانگین‌ها و فاصله اطمینان ۹۵ درصد آن برای پیامد اولیه شمارش گلبول‌های سفید در مقاطع زمانی سیکل‌های اول، دوم، سوم و چهارم:

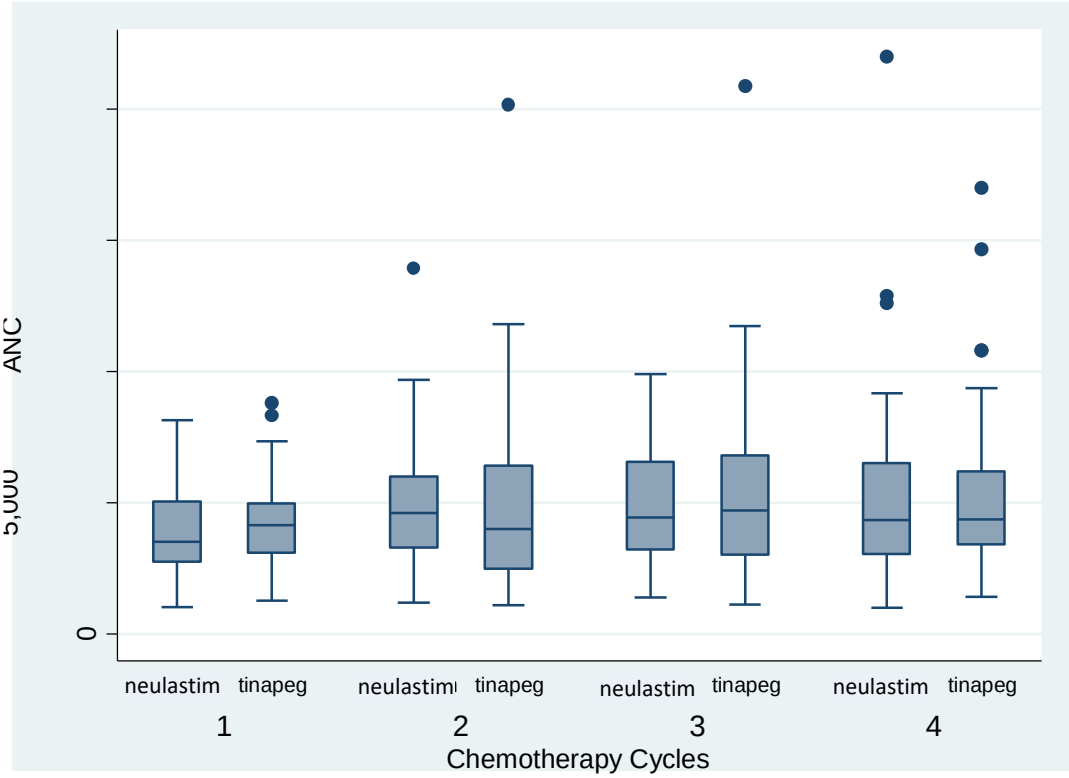
سیکل‌های شیمی درمانی	TinaPeg n (%) (n=51)	Neulastim n (%) (n=51)	Mean Difference (95% CI)	P value
سیکل ۱	7062.9 (1776.1)	7475.3 (4985.0)	-412.4	**0.047**
سیکل۲	7684.7 (3973.3)	8384.9 (3170.8)	-700.2	**0.71**
سیکل۳	7790.7 (3863.9)	7358.7 (2652.1)	432	**0.25**
سیکل۴	7790.9 (3878.17)	7636.3 (3733.4)	154.6	**0.53**

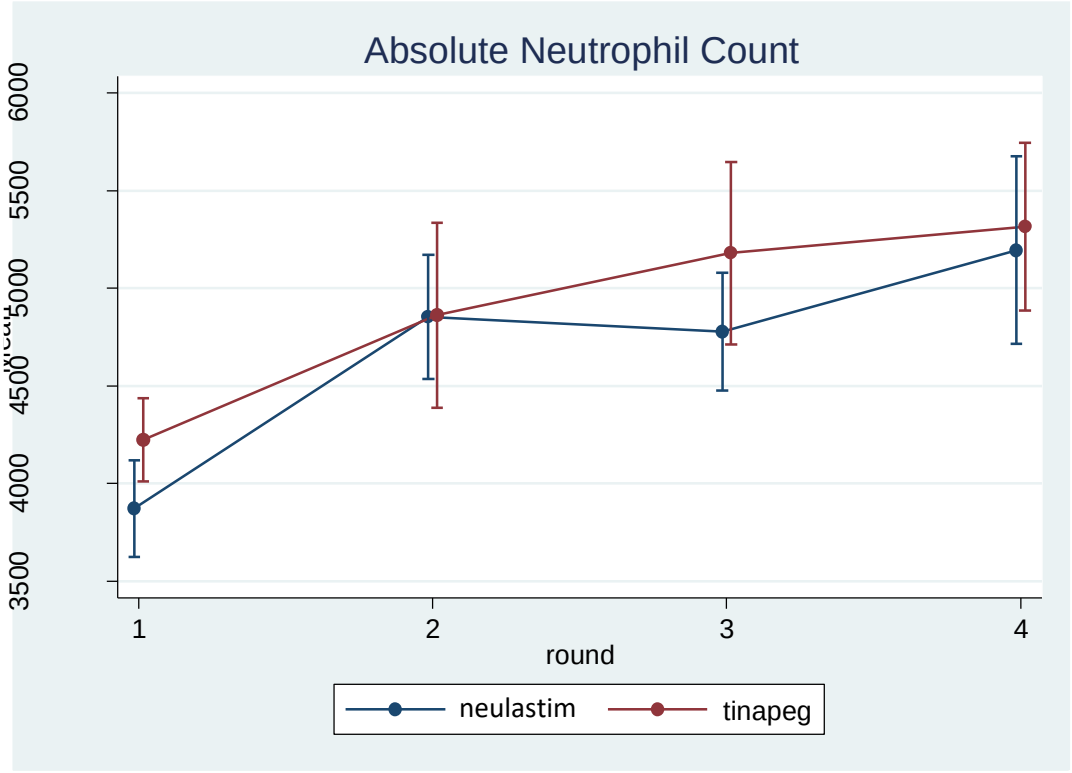
مقادیر عددی در ستونهای مربوط به گروههای درمانی، بصورت mean (sd) می‌باشد.

مقدار عددی شاخص Mean Difference و علامت مثبت یا منفی این شاخص از فرمول $\mathbf{Mean_{TinaPeg} - Mean_{Neulastim}}$ بدست آمده است.

نمودارها:

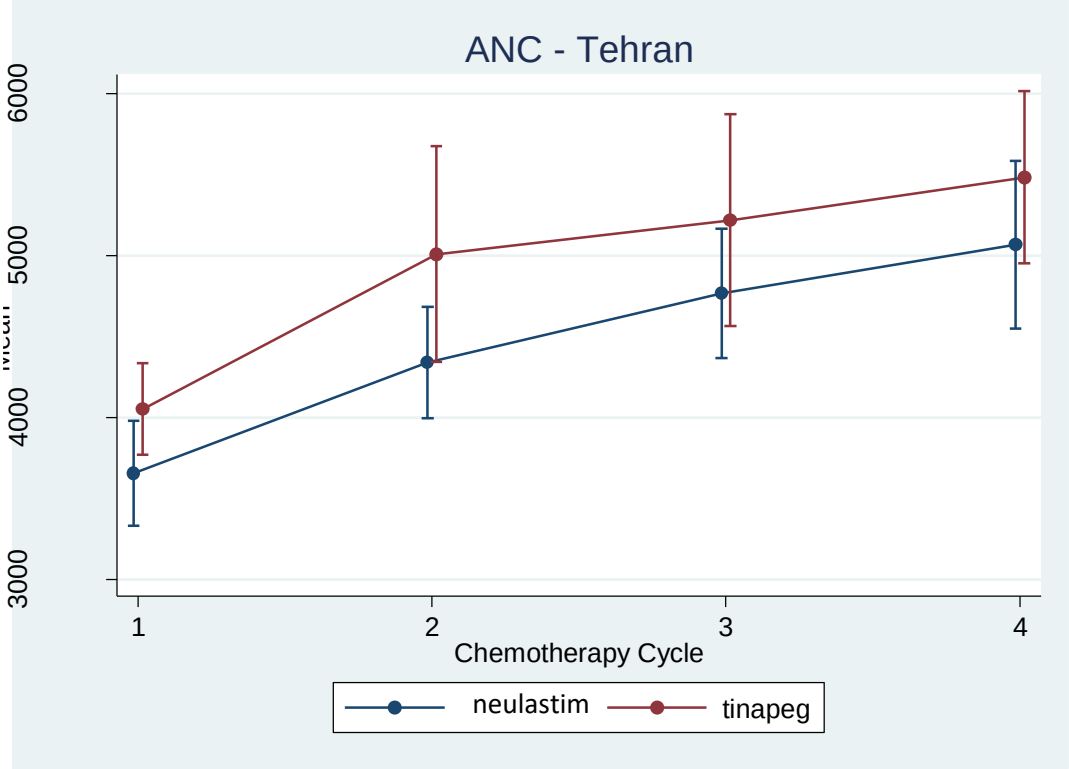
نمودار ۱) نمودار جعبه‌ای ANCدر چهار سیکل شیمی درمانی به تفکیک دو گروه درمانی در کل بیماران تحت مطالعه



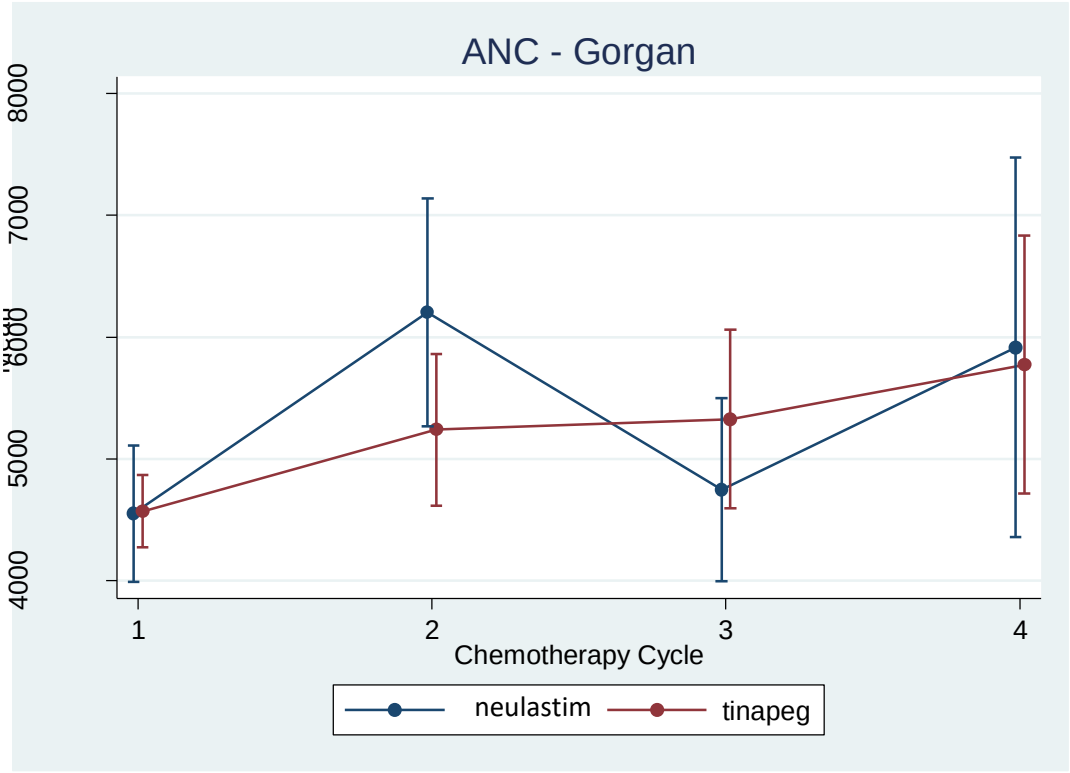


نمودار۲) نمودار توزیع میانگین تغییرات شمارش مطلق نوتروفیل‌ها در چهار دوره درمانی به تفکیک دو گروه

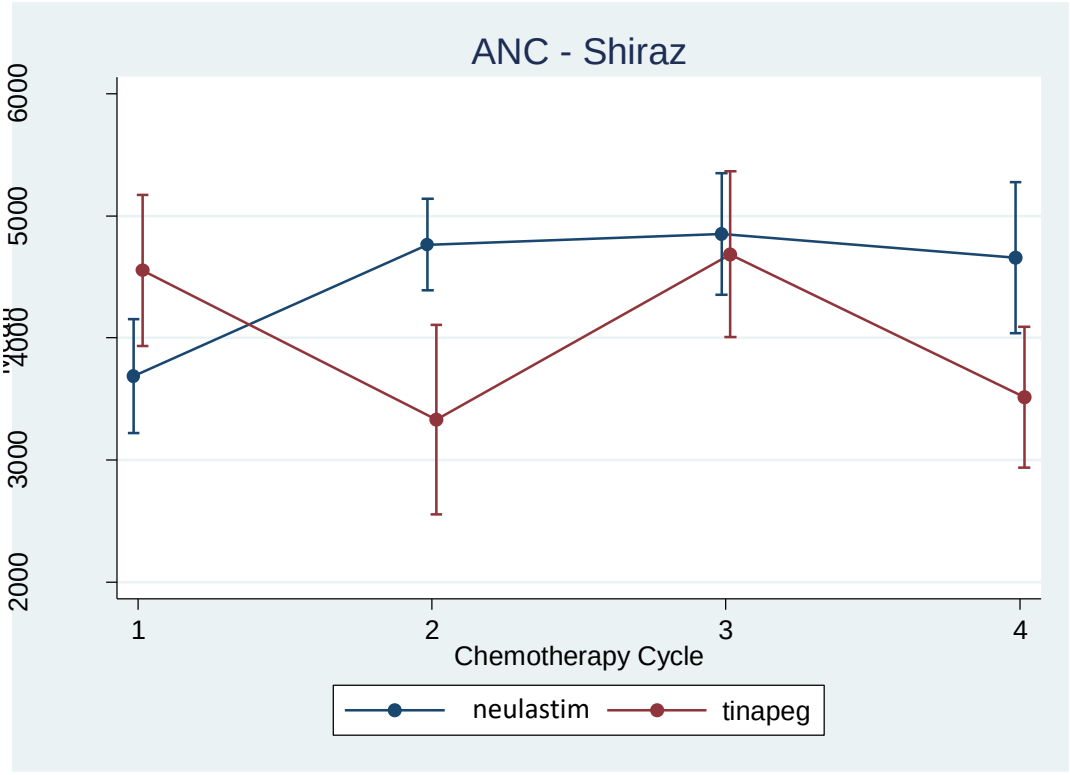
درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد)



نمودار ۳) نمودار توزیع میانگین تغییرات شمارش مطلق نوتروفیل‌ها در چهار دوره درمانی به تفکیک دو گروه درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد) در بیماران مرکز تهران (بیمارستان شریعتی, رسول اکرم ص و فیروزگر)

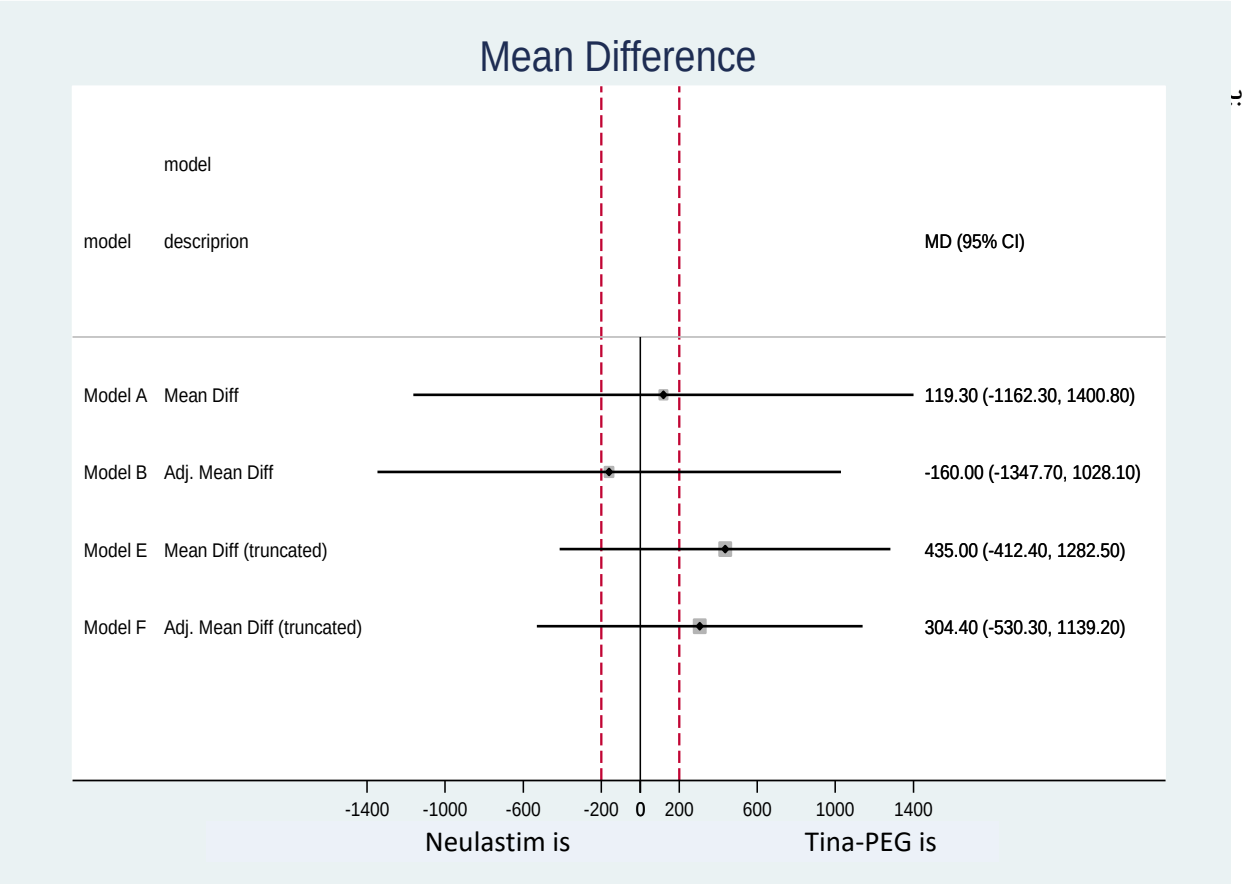


نمودار۴) نمودار توزیع میانگین تغییرات شمارش مطلق نوتروفیل‌ها در چهار دوره درمانی به تفکیک دو گروه درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد) در بیماران مرکز گرگان (بیمارستان ۵ آذر)

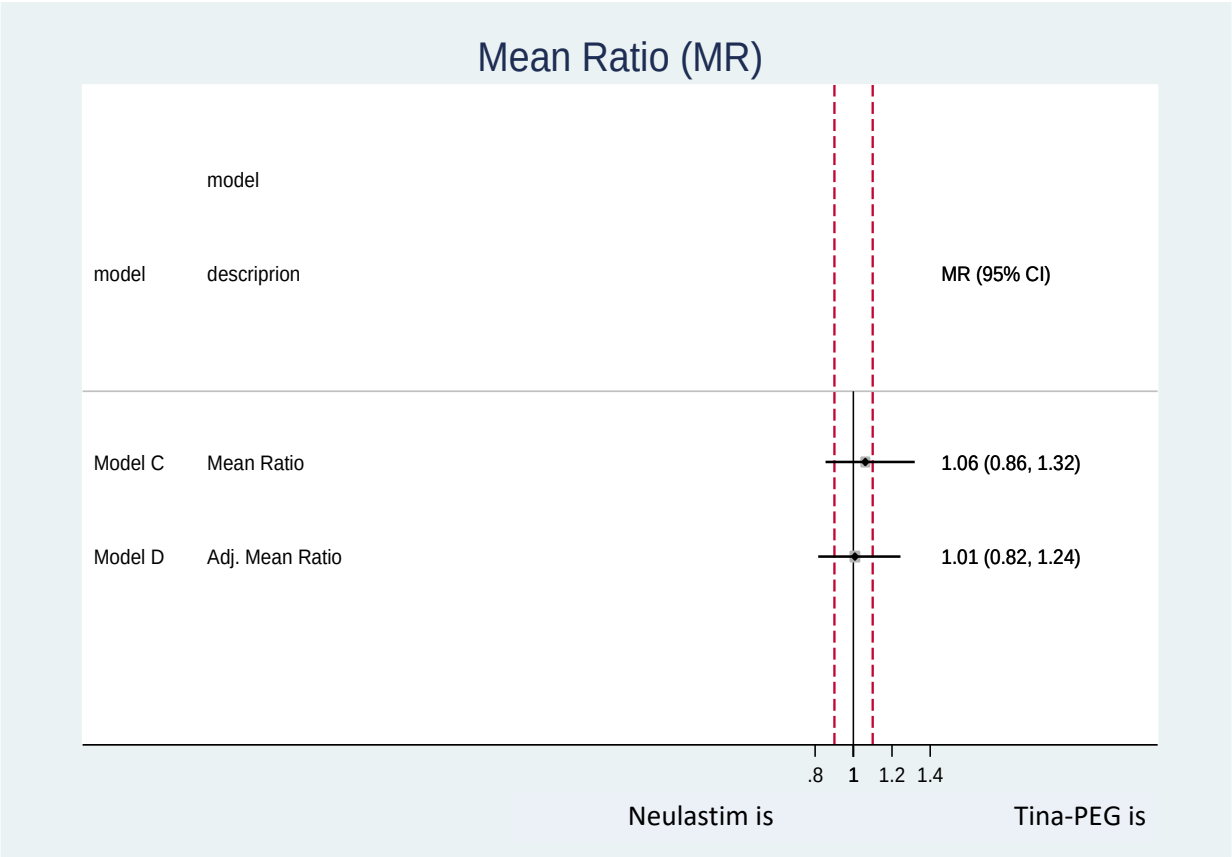


نمودار ۵) نمودار توزیع میانگین تغییرات شمارش مطلق نوتروفیلها در چهار دوره درمانی به تفکیک دو گروه

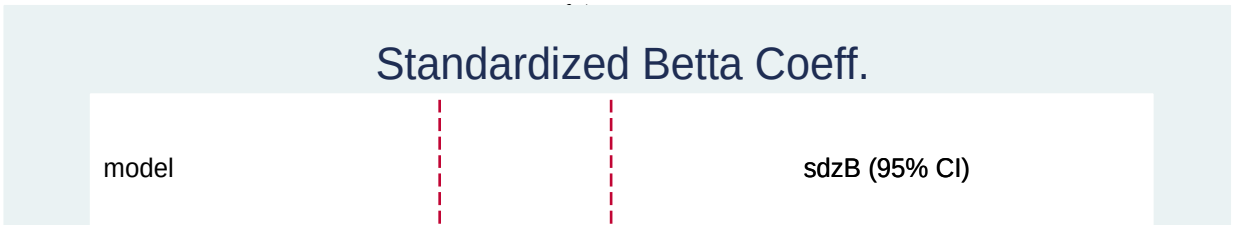
درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد) در



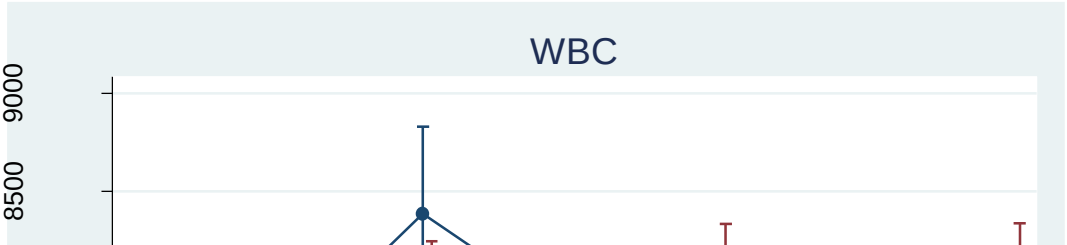
نمودار ۶) نمودار مقایسه نتیجه تحلیل برابری بر اساس شاخص تفاضل میانگین‌ها بر حسب چهار مدل یا رویکرد از مدل‌های ششگانه (توجه نمایید که منطقه بین خطوط – – – نشانگر مارژین برابری می‌باشد)



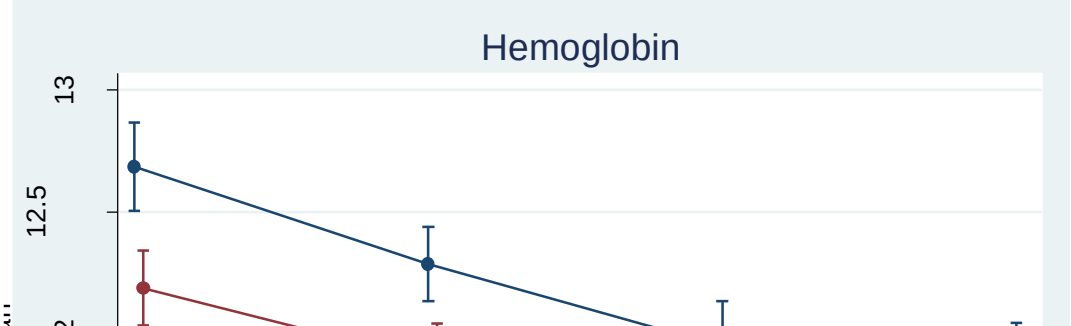
نمودار ۷) نمودار مقایسه نتیجه تحلیل برابری بر اساس شاخص نسبت میانگین‌ها بر حسب دو مدل یا رویکرد از مدل‌های ششگانه (توجه نمایید که منطقه بین خطوط – – – نشانگر مارژین برابری می‌باشد)



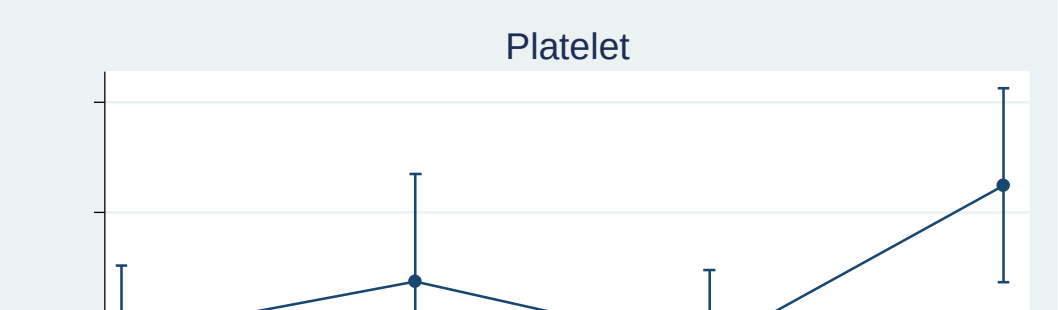
نمودار ۸) نمودار مقایسه اندازه اثر یا قدرت رابطه درمان TinaPeg در مقایسه با درمان Neulastim بر حسب شاخص ضریب بتای استاندارد شده روش تحلیل رگرسیون خطی به تفکیک مدل‌ها یا رویکردهای ششگانه (توجه نمایید که منطقه بین خطوط – – – نشانگر مارژین برابری می‌باشد)



نمودار ۹) نمودار توزیع میانگین تغییرات شمارش گلبول‌های سفید خون در چهار دوره درمانی به تفکیک دو گروه درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد)

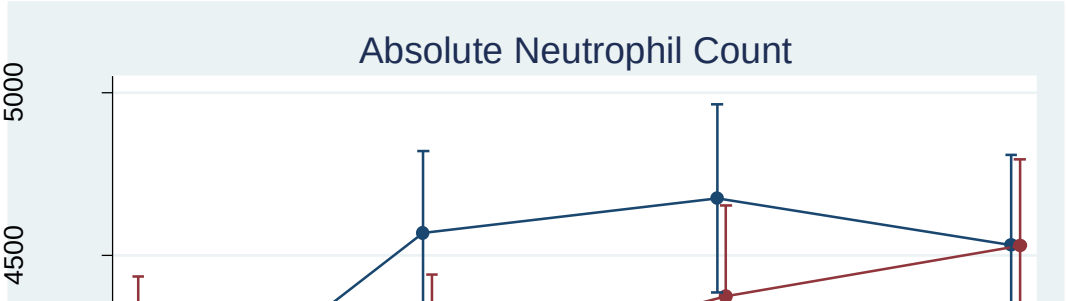


نمودار۱۰) نمودار توزیع میانگین تغییرات هموگلوبین خون (بر حسب گرم در دسی لیتر) در چهار دوره درمانی به تفکیک دو گروه درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد)



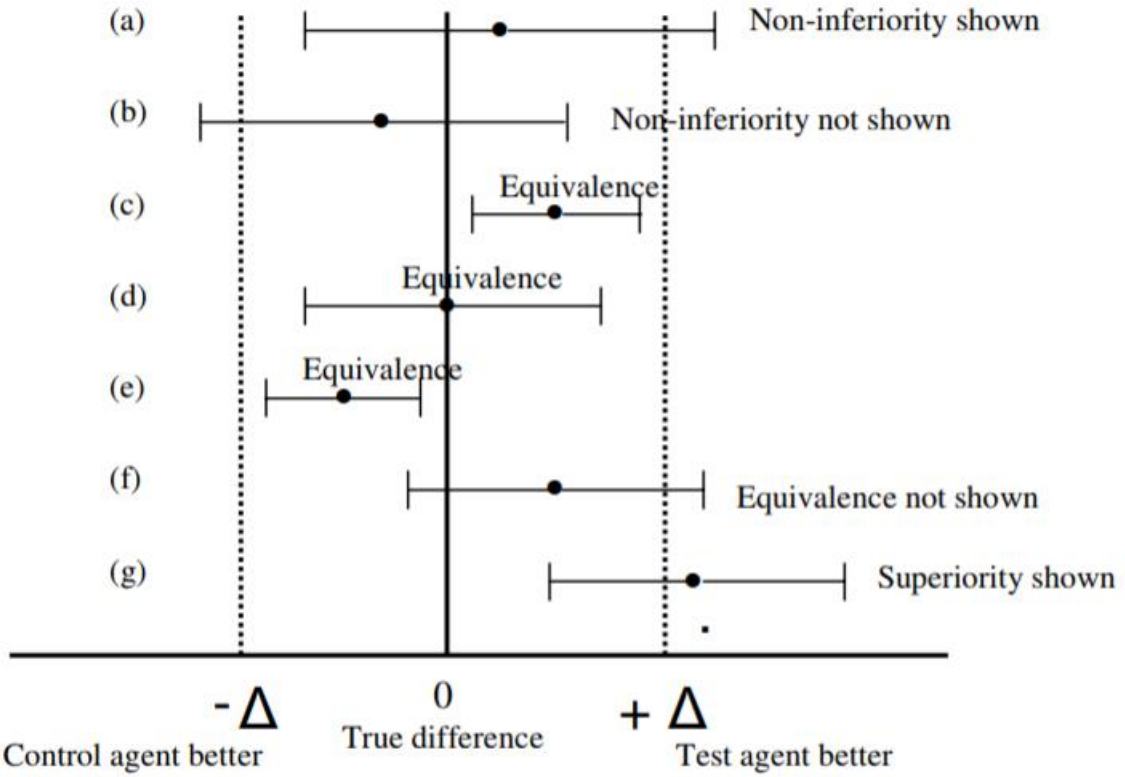
نمودار ۱۱) نمودار توزیع میانگین تغییرات شمارش پلاکت خون در چهار دوره درمانی به تفکیک دو گروه

درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد)

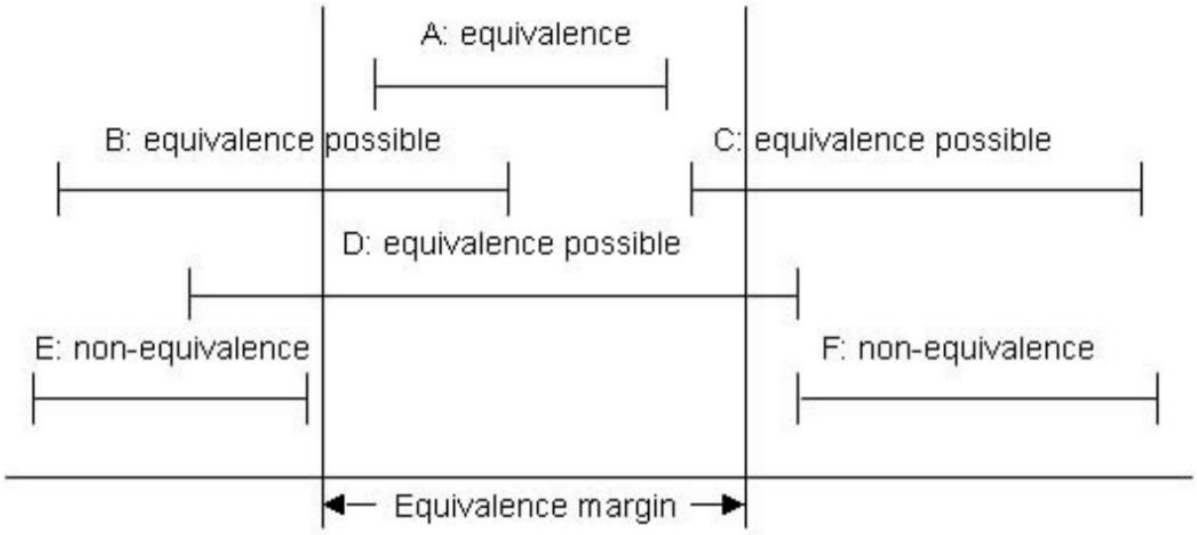


نمودار ۱۲) نمودار توزیع میانگین هرس شده یکطرفه تغییرات شمارش مطلق نوتروفیل‌ها (پس از خارج نمودن ۵٪ مقادیر حداکثری این متغیر بمنظور خارج نمودن داده‌های پرت) در چهار دوره درمانی به تفکیک دو گروه درمانی (تغییرات معادل یک خطا معیار بالاتر و پایین‌تر از مقدار میانگین در هر مقطع زمانی می‌باشد)

تصاویر:



تصویر ۱) آستانه برابری در کارآزمایی‌های برابری به همراه وضعیتهای متفاوت شاخص تصمیم‌گیری (تفاضل میانگین‌ها) و تفسیر هر یک از آنها



تصویر ۲) نمودار شماتیک مفهوم آستانه برابری و جایگاه قرار گیری فاصله اطمینان شاخص تصمیم‌گیری تحلیل برابری (مثال: شاخص تفاضل میانگین) به تفکیک ۶ سناریو مختلف A-F در شرایط مختلف (لازم به ذکر است که در بسیاری از راهنماهای تفسیر یا نگارش مطالعات کارآزمایی بالینی، به سناریوهای B، C و D، حالت‌ها یا تفسیرهای «غیرقطعی» یا Inconclusive Result اطلاق می‌نمایند)

منابع مورد استفاده:

1. Global Cancer Facts and Figures. American Cancer Society. 2nd edition. 2008. [www.cancer.org/acs/groups/content/document/acspc-027766.pdf]
2. https://cancerstatisticscenter.cancer.org/?_ga=1.149380022.1034309583.1464363134#/
3. Chemotherapy Information. [http://www.chemocare.com/whatis/chemotherapy_protocols.asp]
4. Du X, Goodwin JS.Patterns of use of chemotherapy for breast cancer in older women: findings from Medicare claims data. J Clin Oncol. 2001;19(5):1455-61.
5. Harlan LC, Clegg LX, Abrams J, Stevens JL, Ballard-Barbash R. Community-based use of chemotherapy and hormonal therapy for early-stage breast cancer: 1987-2000. J Clin Oncol. 2006;24(6):872-7.
6. Du XL, Osborne C, Goodwin JS. Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. J Clin Oncol. 2002;20(24):4636-42.
7. Nurgalieva Z, Liu CC, Du XL. Chemotherapy use and risk of bone marrow suppression in a large population-based cohort of older women with breast and ovarian cancer. Med Oncol. 2011;28(3):716-25.
8. Metcalf D. The granulocyte-macrophage colony-stimulating factors. Science 1985. 229 (4708): 16–22.
9. Nagata S, Tsuchiya M, Asano S, Kaziro Y, Yamazaki T, Yamamoto O, Hirata Y, Kubota N, Oheda M, Nomura H. Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor. Nature 1986. 319 (6052): 415–8.
10. Souza LM, Boone TC, Gabrilove J, Lai PH, Zsebo KM, Murdock DC, Chazin VR, Bruszewski J, Lu H, Chen KK, Barendt J, Platzer, E, Moore, MAS, Mertelsmann R, Welte K. Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. Science 1986. 232 (4746): 61–5.
11. http://www.rxlist.com/neulasta-drug/warnings-precautions.htm#USP
12. http://www.ingentaconnect.com/content/ben/cpd/2004/00000010/00000011/art00006
13. http://www.drugs.com/pro/neulasta.html
14. Charles L. Vogel,Marek Z. Wojtukiewicz,Robert R. Carroll, Sergei A. Tjulandin, Luis Javier Barajas-Figueroa,Brian L. Wiens,Theresa A. Neumann and Lee S.

Schwartzberg. First and Subsequent Cycle Use of PegFilgrastim Prevents Febrile Neutropenia in Patients With Breast Cancer: A Multicenter, Double-Blind, Placebo-Controlled Phase III Study .JCO February 20, 2005 vol. 23 no. 6 1178-1184.

15. Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon P et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegFilgrastim versus daily Filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol. 2003;14(1):29-35.

16. J.M. Vose ,M. Crump,H. Lazarus, C. Emmanouilides,D. Schenkein, J. Moore,S. Frankel,I. Flinn,W. Lovelace, J. Hackett, B.C. Liang. Randomized, Multicenter, Open-Label Study of PegFilgrastim Compared With Daily Filgrastim After Chemotherapy for Lymphoma.JCO February 1, 2003 vol. 21 no. 3 514-519

17. Matti Aapro,Paul Cornes,Ivo Abraham. Comparative cost-efficiency across the European G5 countries of various regimens of Filgrastim, biosimilar Filgrastim, and pegFilgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia J Oncol Pharm Pract June 2012 vol. 18 no. 2 171-179

18. L. Castagna1, S. Bramanti1,A. Levis2,M. G. Michieli3,A. Anastasia1, R. Mazza1, L. Giordano4,B. Sarina1, E. Todisco1, A. I. Gregorini1 and A. Santoro. PegFilgrastim versus Filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support.Ann Oncol (2010) 21 (7): 1482-1485.

19. Harold J. Burstein, Leroy M. Parker, Aparna Keshaviah, Jennifer Doherty, Ann H. Partridge,Lidia Schapira, Paula D. Ryan, Jerry Younger, Lyndsay N. Harris, Beverly Moy, Steven E. Come,Susan T. Schumer, Craig A. Bunnell, Margaret Haldoupis, Rebecca Gelman, and Eric P. Winer. Efficacy of PegFilgrastim and Darbepoetin Alfa as Hematopoietic Support for Dose-Dense Every-2-Week Adjuvant Breast Cancer Chemotherapy. J Clin Oncol. 2005 Nov 20;23(33):8340-7

20. Kourlaba G[1], Dimopoulos MA, Pectasides D, Skarlos DV, Gogas H, Pentheroudakis G, Koutras A, Fountzilas G, Maniadakis N.Comparison of Filgrastim and pegFilgrastim to prevent neutropenia and maintain dose intensity of adjuvant chemotherapy in patients with breast cancer. 2015 Jul;23(7):2045-5

21. Porta N, Bonet C, Cobo E. Discordance between reported intention-to-treat and per protocol analyses. J Clin Epidemiol. 2007; 60(7):663-9.

22. A Randomized parallel group clinical trial to determine the effectiveness, safety and tolerability of Actoverco Filgrastim and Actoverco PegFilgrastim compared to Neupogen® for prevention of chemotherapy induced neutropenia in the treatment of the breast cancer. Irct registration number : IRCT2013042212398N4

23. Laura Biganzoli, Michael Untch, Tomas Skacel, and Jose´-Luis Pico .Neulasta (PegFilgrastim): A Once-Per-Cycle Option for the Management of Chemotherapy-Induced Neutropenia.Semin Oncol. 2004 Jun;31(3 Suppl 8):27-34

24. RL Jones1, G Walsh1, S Ashley1, S Chua1, R Agarwal1, M O'Brien1, S Johnston1,2 and IE Smith*, A randomised pilot Phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegFilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer, British Journal of Cancer (2009) 100, 305 – 310

25. Harold J. Burstein, MD, PhD . Myeloid Growth Factor Support for Dose-Dense Adjuvant Chemotherapy for Breast CancerOncology (Williston Park). 2006 Dec;20(14 Suppl 9):13-5

26. Schuirmann, Donald J. "A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability." Journal of pharmacokinetics and biopharmaceutics 15.6 (1987): 657-680.

27. Walker, Esteban, and Amy S. Nowacki. "Understanding equivalence and noninferiority testing." Journal of general internal medicine 26.2 (2011): 192-196.

28. Bennett, C.L., et al., Use of hematopoietic colony-stimulating factors: comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines. Journal of clinical oncology, 1999. 17(11): p. 3676-3681.

29. Smith, T.J., et al., 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. Journal of Clinical Oncology, 2006. 24(19): p. 3187-3205.

30. Sung, L., et al., Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Annals of internal medicine, 2007. 147(6): p. 400-411.

31. Smith, T.J., et al., Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. Journal of Clinical Oncology, 2015. 33(28): p. 3199-3212.

32. Godwin, J.E., et al., A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). Blood, 1998. 91(10): p. 3607-3615.

33. Thatcher, N., et al., Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: Results of a British Medical Research

Council multicenter randomized trial. Journal of clinical oncology, 2000. 18(2): p. 395-395.

34. García-Carbonero, R., et al., Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. Journal of the National Cancer Institute, 2001. 93(1): p. 31-38.

35. Del Giglio, A., et al., XM02 is superior to placebo and equivalent to Neupogen™ in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC cancer, 2008. 8(1): p. 332.

36. Waller, C.F., et al., A phase III randomized equivalence study of biosimilar Filgrastim versus Amgen Filgrastim in patients receiving myelosuppressive chemotherapy for breast cancer. Oncology Research and Treatment, 2010. 33(10): p. 504-511.

37. Beksac, M., et al., Short and long term effects of granulocyte colony-stimulating factor during induction therapy in acute myeloid leukemia patients younger than 65: Results of a randomized multicenter phase III trial. Leukemia research, 2011. 35(3): p. 340-345.

38. Ruiz, L.P., et al., Efficacy and safety of ior® LeukoCIM (G-CSF) in patients with neutropenia after chemotherapy. Rev Cubana Farm, 2011. 45(1): p. 19-33.

39. Sagara, Y., et al., The efficacy and safety of FSK0808, Filgrastim Biosimilar: a multicenter, non-randomized study in Japanese patients with breast cancer. Japanese journal of clinical oncology, 2013: p. hyt091.

40. Blackwell, K., et al., Comparison of EP2006, a Filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Annals of Oncology, 2015. 26(9): p. 1948-1953.

41. Sandoz launches ZarxioTM (Filgrastim-sndz), the first biosimilar in the United States. 2015; Available from: https://www.novartis.com/news/media-releases/sandoz-launches-zarxiotm-Filgrastim-sndz-first-biosimilar-united-states.

42. Moafi, A., et al., Comparing efficacy and side effects of Pd-Grastim and Neupogen for prevention of neutropenia after chemotherapy in children. 2007.

43. Meyer, M.C., Applied biopharmaceutics and pharmacokinetics. By Leon Shargel and Andrew BC YU. Appleton-century-crofts, 292 madison ave., NEW YORK, NY 10017.1980. 253 pp. 16× 24 cm. price $18.50. Journal of Pharmaceutical Sciences, 1981. 70(10): p. 1179-1179.

44. Filgrastim information from DrugsUpdate,Medical Books. Available from: http://www.drugsupdate.com/generic/view/168/Filgrastim.

45. EHSANI, M., et al., Evaluation of efficacy and side effects of FILGRASTIM versus PD-Grastim in prevention of neutropenia in patients with neuroblastoma under treatment with OPEC chemotherapy protocol–A Comparative Study. 2006.

46. Filgrastim. Available from: http://fa.search.irct.ir/.

47. Gatzemeier, U., et al., XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. Journal of Thoracic Oncology, 2009. 4(6): p. 736-740.

48. Engert, A., et al., XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leukemia & lymphoma, 2009. 50(3): p. 374-379.

49. Furberg, Curt D., and Lawrence M. Friedman. "Approaches to data analyses of clinical trials." Progress in cardiovascular diseases 54.4 (2012): 330-334.

50. Lang, Thomas A., and Douglas G. Altman. "Basic statistical reporting for articles published in biomedical journals: the “Statistical Analyses and Methods in the Published Literature” or the SAMPL Guidelines”." Handbook, European Association of Science Editors 256 (2013): 256.

51. Bland, J. Martin, and Douglas G. Altman. "Comparisons against baseline within randomised groups are often used and can be highly misleading." Trials 12.1 (2011): 264.

52. Altman, Douglas G. "Comparability of randomised groups." The Statistician (1985): 125-136.

53. Bland, J. Martin, and Douglas G. Altman. "Comparisons within randomised groups can be very misleading." Bmj 342 (2011): d561.

54. Vickers, Andrew J., and Douglas G. Altman. "Analysing controlled trials with baseline and follow up measurements." Bmj 323.7321 (2001): 1123-1124.

55. Bland, J. Martin, and Douglas G. Altman. "Best (but oft forgotten) practices: testing for treatment effects in randomized trials by separate analyses of changes from baseline in each group is a misleading approach." The American journal of clinical nutrition 102.5 (2015): 991-994.

56. Sun, Wanjie, Stella Grosser, and Yi Tsong. "Ratio of means vs. difference of means as measures of superiority, noninferiority, and average bioequivalence." Journal of biopharmaceutical statistics 27.2 (2017): 338-355.

57. FDA. Guidance on Bioavailability and Bioequivalence Studies for Orally Administrated Drug Products – General Considerations. Center for Drug Evaluation and Research, the US Food and Drug Administration; Rockville, Maryland, USA: 2003.

58. Wilcox, Rand R. Introduction to robust estimation and hypothesis testing. Academic press, 2011.

59. Chen, Ling. "A one-sided trimmed mean estimator for the mean of positively skewed distributions." Australian Journal of Statistics 37.3 (1995): 313-322.

60. Flight, Laura, and Steven A. Julious. "Practical guide to sample size calculations: non-inferiority and equivalence trials." Pharmaceutical statistics 15.1 (2016): 80-89.

61. Cohen, Jacob, et al. "Applied multiple regression/correlation analysis for the behavioral sciences." (1983). P.51-52