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WORKSHOP

Breakthrough in supportive cancer care: introducing Pegfilgrastim

Rome, 8 november 2003

Guest Editors: Sergio Amadori, Sante Tura

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The origin and power of a name

Ancient Greek

αιμα [aima] = blood;
αιματος [aimatos] = of blood,
λογος [logos]= reasoning

Scientific Latin

haematologicus (adjective) = related to blood

Scientific Latin

haematologica (adjective, plural and neuter, used as a noun) = hematological subjects

Modern English

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Breakthrough in supportive cancer care: introducing Pegfilgrastim

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Ethiopathogenesis and incidence of neutropenia

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According to WHO's (World Health Organization) common toxicity criteria, we can define four grades of neutropenia, on the basis of counting absolute neutrophil (ANC): mild (grade 1), moderate (grade 2); severe (grade 3) and life-threatening (grade 4). Moreover, the term febrile neutropenia (FN) is referred to condition of raised temperature (>38.8°C) in presence of severe neutropenia (ANC 0,5-1.0x10^9/L); life-threatening sepsis is possible in these conditions (Figure 1).

Chemotherapy inducing grade 3-4 neutropenia (CIN) is common in clinical practice; in addition to increasing the risk of life-threatening infections and consequent hospitalisation rate and use of intravenous antibiotics; grade 3-4 neutropenia (CIN), might cause chemotherapy delays and dose reductions. CIN has an important impact on patient quality of life and on health economic costs due to treatment.[1-5]

The reported incidence of grade 3-4 leukopenia varies widely in different studies, even considering the same or similar chemotherapy regimens. This issue emerged in a systematic survey of large randomized trials, carried out between 1990-2000, in patients treated with chemotherapy for non-Hodgkin's lymphoma (LNH) or early-stage breast cancer. Grade 3-4 leukopenia was 8% to 51% with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), 1% to 78% with CMF (cyclophosphamide, methotrexate, fluorouracil) and 3% to 100% with CAF (cyclophosphamide, doxorubicin, fluorouracil) and FEC (fluorouracil, epirubicin, cyclophosphamide) regimens.

Therefore, although myelosuppression has been shown as a common side effect of chemotherapy, is not still possible to assigne a specific risk to many different commonly used regimens.[1]

The occurrence of neutropenia and its complications are very common with standard dose chemotherapy regimens: febrile neutropenia is the most frequent manifestation, regarding about 0-57% of treated population, following severe neutropenia (2-28%) and severe infections (0-16%); the estimate of mortality rate, during febrile neutropenia, was about 0% to 7% in some studies.[6]

The risk of CIN occurrence, depends on how long chemotherapy is given. In a retrospective analysis of a cohort of 577 patients treated with CHOP for NHL, for example, the overall risk for CIN increased with the number of delivered cycles: the incidence was up to 15% during the first twenty days of treatment and continued to rise in all subsequent cycles to an overall risk of 30% five months later. The incidence of febrile neutropenia could depend on the age of treated patients: considering different age ranges, the risk was significantly higher in elderly patients (more than 65 years) when compared to younger patients (p=0.0002).[7]

In addition to age, the risk for CIN is influenced by other underlying factors such as baseline anaemia severity, coexistent heart and renal diseases, planned reduced dose index (RDI) and no use of colony stimulating factors (CSF). A retrospective analysis of a cohort of patients with NHL treated with CHOP revealed that, based on 6 risk factors identified from the study, patients can be grouped according to the risk of febrile neutropenia. The risk of CIN increased with the increasing of the risk score: patients with 5–6 of the risk factors, were at almost 60%-risk of suffering an episode of febrile neutropenia during their treatment (Figure 2).[7]

The management of CIN determines a remarkable impact on economic costs, due mainly to hospitalisation costs: a retrospective analysis on over 55,000 patients from USA, revealed that the average admission for CIN was of six days (mean 11.21 days).[8]

The relevant problem of bacterial infections during CIN, and their treatement, has been evaluated in the prospective randomised EORTC-IATCG XI Trial, conducted on over 900 patients in 1996, comparing two different antibiotic treatment arms: meropenem versus ceftazidime plus amikacin combination. The average period of granulocytopenia before study entry was 5 days in

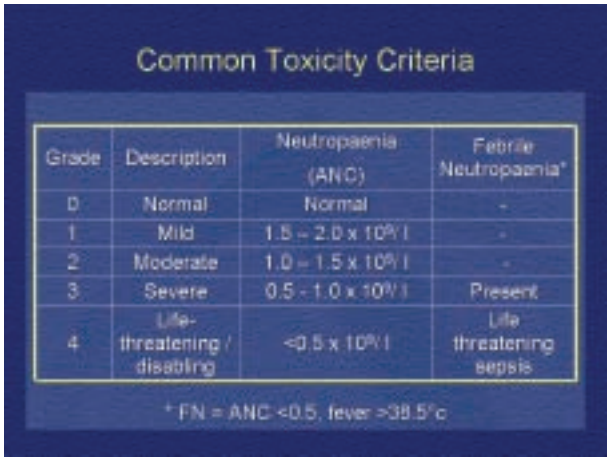

Figure 1. Common toxicity criteria.

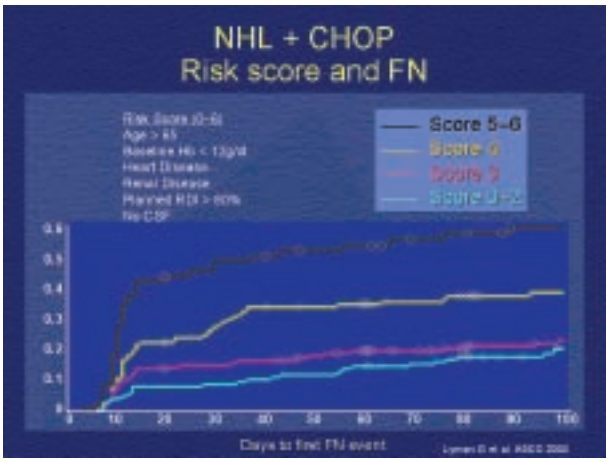

Figure 2. NHL+CHOP: risk score and FN.

both arms; the total days of granulocytopenia period were 16 days (range 1-179) in meropenem arm and 17 days (range 2-78) in combination arm. Response to antibiotic treatment was reached in 56% of patients in monotherapy and in 52% of patients in combination therapy, with an average time to defervescence of 3 days and 5 days, respectively (p=0.07). Nevertheless, a high proportion of patients did not respond to treatment and presented a persistent CIN in the study. Reasons for antibiotic modification, were mainly persistent fever, antibiotic-resistance pathogen, progression of infection, relapsing fever, presence of fever spikes, breakthrough or persistent bacteremia, toxicity of therapy, viral or fungal infection, development of septic shock. According to microbiological identification, infection had been documented in 254 patients and in half of them (54%) the pathogen was a single gram-positive organism: methicillin-sensitive (9.8%) or methicillin-resistant (19.7%) coagulase-negative staphylococci, *Staphylococcus aureus* (4.3%), streptococci (15.4%); infection was caused by gram-negative pathogens in 24% of cases, mainly *Escherichia coli* (11.8%), *Pseudomonas aeruginosa* (3.1%), *Klebsiella spp.* or *Enterobacter spp.* (2.0%); polymicrobial infection was identified in 1.1% of cases. Identification of fever origin was not possible in 442 patients.[9]

Fungal infections are a relevant concern in CIN. A clinical trial compared voriconazole (415 patients) versus ambisome treatment (422 patients) in 800 patients. Median length of neutropenia at study entry was 7.7 (range 2.4-71) and 7.6 (range 2.4-60) days, respectively; overall neutropenia period was 15.2 and 14.2 days respectively in two treatment arms. Microbiological identification was possible in 3.4% patients; responsible pathogen was *Aspergillus spp.* (infection sites: 44.8% lungs, 6.9% sinuses, 3.7% central nervous system or skin, and 3.7% disseminated) in 58.6% of cases, *Candida spp.* (infection sites: 3.7% disseminated infections and 24.1% blood) in 27.6% of cases, zygomycetes in 6.9%, and dematiaceus mold in 6.9% of cases.[10]

Neutropenia affects tumor cure or response rate to chemotherapy too, in addition to its impact on quality of life.

The *United Kingdom Neutropenia Audit* in a multicenter trial (a total of 8 centres) studied 177 patients treated with chemotherapy for lymphoma. For LNH chemotherapy, regimens were CHOP in 73% of cases and PMitCEBO (mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine) in 19% of cases; for patients with Hodgkin's disease (HD) treatment regimen was ABVD (adriamycin, bleomycin, vincristine, doxorubicin) in 60% of cases. Neutropenic events, such as: CIN requiring hospitalisation, chemotherapy more-than-a-week dose delay or a dose reduction >15%, were all recordered. High rates of overall neutropenic events were observed with all used chemotherapy regimens, although the incidence was higher with ABVD regimens: 68% with ABVD versus 52% with PMitCEBO and 28% with CHOP regimen. Chemotherapy administration delays were observed in 64%, 38% and 15% of cases respectively with three treatment regimens. Thirty-five percent of patients treated with PMitCEBO and 7% of those treated with other two regimens, needed a chemotherapy dose reduction. CIN events requiring hospitalisation, were mainly observed in patients with CHOP (12%) and PMitCEBO (14%) treatment regimens. Chemotherapy dose reduction was more likely in patients with neutropenic events than patients with no events: dose reduction ranged from 96% to 88.1% (p=0.05) in first line CHOP treatment, from 93.6% to 85.3% (p=0.05) in PMitCEBO regimen, and from 95.1% to 81.2% (p=0.01) in ABVD regimen. Furthermore, patients experiencing a neutropenic event were at high risk of developing a subsequent event: the risk was 31.6% in patients treated with CHOP or MCOP (replace-

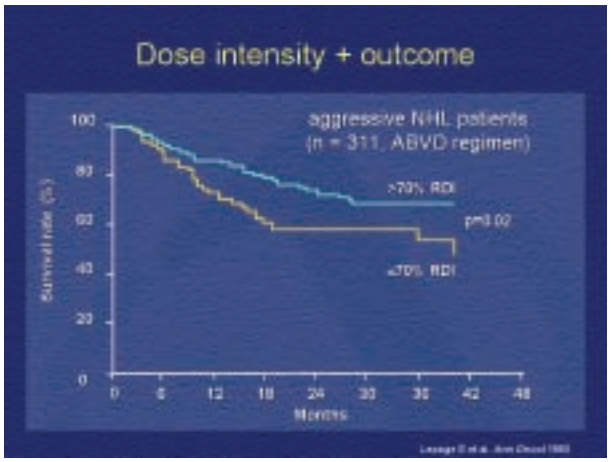

Figure 3. Dose intensity and outcome.

ment of doxurubicin with mitoxantrone), 38.5% during treatment with PMitCEBO, PACEBO, PACEBOM (cyclophosphamides, doxorubicin, etoposide, alterning vincristine, bleomycin, methotrexate), and 69.2% in patients with ABVD.

In conclusion, *United Kingdom Lymphoma Neutropenia Audit* analysis demonstrated that a high percentage (43%) of patients treated with chemotherapy for lymphoma experience a neutropenic event: in detail, 68% of patients with HD and 34% of patients with LNH. Twenty-nine percent of patients experiencing a neutropenic event receive a chemotherapy dose reduction >15%; in this context, the administration of granulocyte-colony stimulating factors (G-CSF) allows to delivery planned dose intensity. Finally, after a first neutropenic event, patients are at high risk to develop a subsequent event: this risk is about 31% during CHOP regimen and 69% during ABVD regimen.[11]

The ability of delivering a full dose chemotherapy is a determinant concern in lymphoma treatment management in order to achieve a therapeutic success. A retrospective analysis on over 300 patients under 55 years of age with aggressive LNH treated with ABVD chemotherapy showed that administrating <70% of planned dose was associated with significantly inferior survival rates than administration of >70% planned (two-years survival rates 61% versus 72%, respectively; p = 0.02) (12) (Figure 3).

Other literature data, showed that when patients receive full dose chemotherapy from the beginning, their age does not affect the survival estimates. In an analysis comparing different chemotherapy regimens, the 5-year survival rate was similar for >60 and <60 years age groups: 41% and 49% respectively (p=0.22).[13] These data indicate that delivering full dose chemotherapy to elderly patients allows to achieve a therapeutic success even in this patients' group.

In conclusion, the occurrence of neutropenia, which commonly affects cancer patients treated with chemotherapy, is often under reported and underestimated as side effect of chemotherapy. The correct management of neutropenia is determinant considering its adverse impact on quality of life, on therapeutic outcome, on morbidity and mortality rates, and on health economic costs.

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Guidelines in the treatment of neutropenia

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The criteria to formulate guidelines for using myelopoietic growth factors in oncologic patients are based on several potential benefits described in literature: reduction of infections rates, improved cancer outcome, mortality reduction, cost reduction, improvement of function and quality of life. Data related to real benefit on survival are discordant, due to studies design; available data come from clinical trials which generally select patients with better performance status and curable malignancies.

In a randomized, placebo-controlled, USA Pilot Study, on patients with small cell lung cancer, filgastrim was associated with a significant reduction of neutropenic infections related both to first course (57% in placebo arm versus 28% in treatment arm; p<0.001) and cumulative incidence (77% versus 40% respectively; p<0.001). Incidence of culture confirmed infections was reduced of about 50%, too. Thus, the administration of filgrastim allows to delay the occurrence of infections during neutropenia period, even if its risk is not eliminated (Figure 1).[1]

Similar results were observed in an European Pilot Study, in which administration of filgrastim significantly reduced febrile neutropenia incidence both related to first chemotherapy cycle (20% in treatment group versus 41% in placebo group; p<0.012) and cumulative incidence (26% versus 53%, respectively; p<0.002) and was associated with a slight reduction of culture-confirmed infections (20% versus 33% in placebo arm; p=<0.1). In filgrastim group, the proportion of patients requiring a chemotherapy dose delay >2 days (29% versus 47% in placebo arm; p<0.04) or a planned dose reduction (29% versus 61% in placebo arm; p<0.0001) was reduced (Figure 2).[2]

In a meta-analysis selecting 8 studies concerning patients with lymphoma or solid tumours, a total of 1,144 patients have been evaluated, with an average of 143 patients for each trial (range 48-257), with Jadad quality score of 3.38 (range 3-4). In the studies the use of colony stimulating factors, filgrastim or lenograstim, had been compared with placebo. Each trial demonstrated the efficacy of colony stimulating factors administration on reduction of febrile neutropenia risk; risk reduction was 0.38 (p<0.001) in the overall studies analysis (Figure 3). Meta-analysis results did not show a difference between studies referring to placebo control (febrile neutropenia risk 0.35 in placebo-controlled trials and 0.47 in untreated control), or to malignancy type. Considering the two different colony stimulating factors, filgrastim seemed to be more effective, allowing a risk reduction of 0.34 versus 0.48 in lenograstim groups. In addition to febrile neutropenia risk reduction, analysed trials showed that administration of colony stimulating factors was significantly associated with reduced risk of documented infections (OR=0.51; p<0.001) and of mortality related to infections (OR=0.60; p=0.16) as well.[3]

Patients age represents a remarkable risk factor for febrile neutropenia. In a retrospective analysis of 577 patients with non-Hodgkin's lymphoma (NHL) under chemotherapy, 62% of febrile neutropenia events were observed in patients over 65 years of age; moreover, in this patients group the time to febrile neutropenia occurrence was shorter determining consequently a higher risk of infections during early phases of chemotherapy treatment.[4] Considering the use of colony stimulating factors, filgrastim or pegfilgrastim, the impact on survival and on quality of life of patients should be taken into account.

Even if available literature data from clinical studies do not show a direct effect of filgrastim on survival in patients with lymphoma, neither in elderly population, nevertheless the efficacy on neutropenia reduction has been clearly demonstrated.

Age, is a negative prognostic factor that affects the occurrence of febrile neutropenia and patients mortality, as shown in a study performed by Kuderer *et al.*, analysing

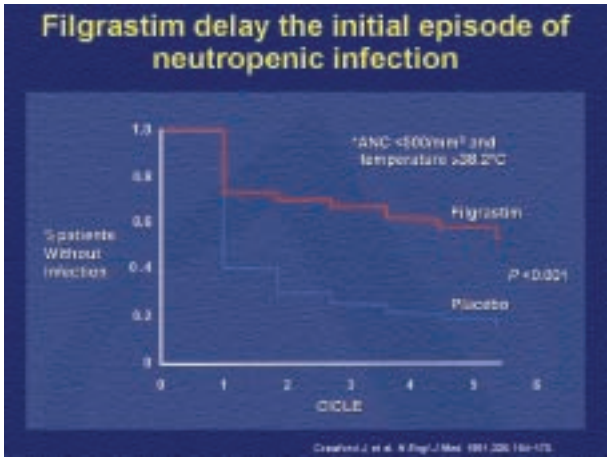

Figure 1. Filgrastim delay the initial episode of neutropenic infection.

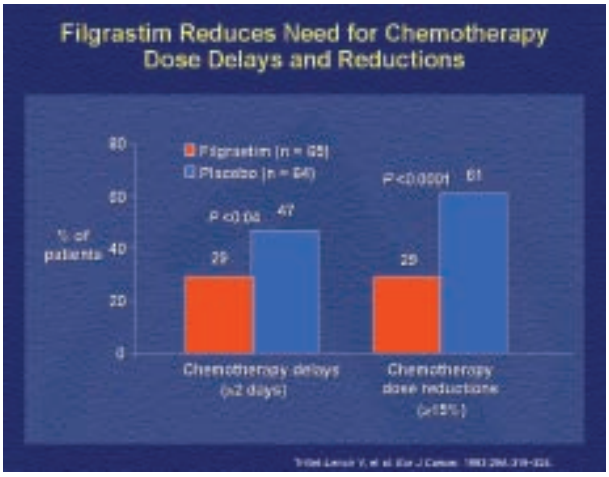

Figure 2. Filgrastim reduces need for chemotherapy dose delays and reductions.

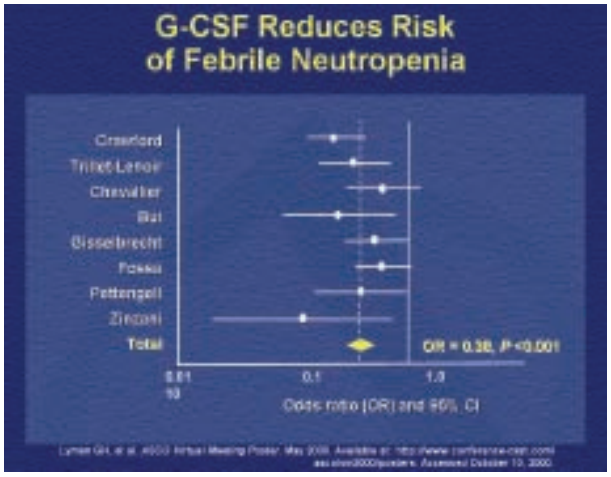

Figure 3. G-CSF reduces risk of febrile neutropenia.

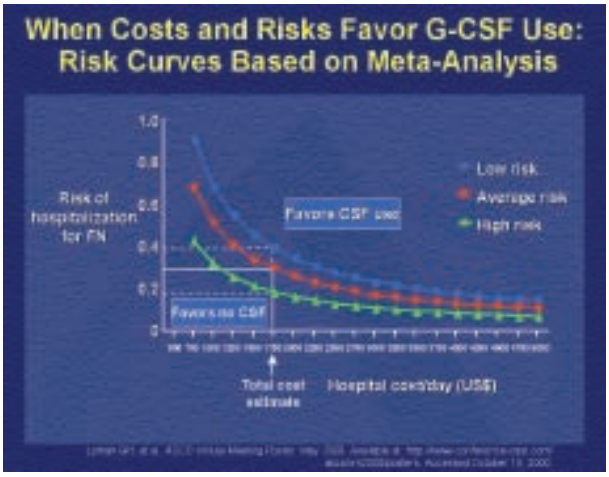

Figure 4. Risk curves based on meta-analyses.

data relative to 41,779 hospital admissions due to febrile neutropenia in cancer patients during the period 1995-2000: mortality rate showed an increasing linear trend according to progressive age groups (t-test for trend p<0.001).[5] Chemotherapy dose reduction in elderly patients, in order to reduce neutropenia occurrence and its complications, seems not to be a promising strategy, mainly in NHL patients.

Considering all treated patients population, a significant difference was noticed between different age groups with reference to clinical response: this was 65% in <40 years, 60% in 40-54 years, 55% in 55-64 years and 37% in >65 years age patient group. Nevertheless, when considering only patients treated with full dose chemotherapy, complete response rate were higher and similar between different patients groups. Besides, this therapeutic advantage was more evident in elderly patients: response rates were 68%, 64%, 57% and 52% respectively for the different age groups.[6]

Elderly patients with aggressive-histology non-Hodgkin's lymphoma, could take advantages by adequate and specific treatment regimens. Delivering full dose VNCOP-B (cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin e prednisone) regimen to patients >60 years was associated with a similar response rate between different age groups: 61% in patients 60-69 years old, 59% in those 70-79 years and 56% in patients >80 years.[7]

In CALGB 8541 clinical trial, patients with unilater-

al breast cancer were treated with three different chemotherapy dose intensity regimens: standard (dose and dose intensità double than low dose arm); moderate (dose intensity as much as 2/3 high dose arm but with equal total dose), and low dosage. After a 9-year follow-up, high and moderate dose regimens were associated with a better disease free survival ($p<0.0002$) and overall survival rates (respectively 79%, 77% e 72%; $p<0.0034$) than low dose regimen.[8]

The use of filgrastim allows to replace sequential chemotherapy regimens with concurrent chemotherapy regimens, by reducing chemotherapy induced myelosuppression; therefore, intervals between cycles could be reduced, dose density could be increased, with consequent increased treatment effectiveness. In a recent clinical trial of patients with breast cancer, a dose-dense combination chemotherapy regimen (cyclophosphamide (A), doxorubicin (C) e paclitaxel (T)) had been compared to a conventional sequential regimen using the same drugs (A-T-C); two regimens were delivered every three or two weeks (4 treatment arms), supporting 14 days-regimens with prophylactic administration of filgrastim. After a median 36-month follow-up, in interim analysis *dose-dense* regimens were associated with higher proportion of disease-free survival (82% versus 75%) and overall survival (92% versus 90%) rate than the same regimens delivered as conventional protocol of 21 days.[9]

Studies on chemotherapy dose density have been performed in patients with lymphoma too; delivering CHOP cycles every two weeks in association with G-CFS prophylaxis, seemed to be associated with higher complete remission rates (77% versus 63,2%; $p=0.009$) and 40-months survival rates (64,3% versus 49%; $p=0.04$) than conventional 21 days schedule.[10]

The impact of neutropenia on patient quality of life is a further important aspect that should be considered when dealing with neutropenia. Neutropenia is associated with symptoms such as general malaise, pain, treatment-related symptoms. In addition, quality of life is heavily influenced by hospitalization, which mainly in elderly patients, determinates medical complications and function compromise.

Several small sample trials have studied the impact of neutropenia on quality of life with Cancer Care Monitor instrument, showing a correlation between chemotherapy induced neutropenia and quality of life compromission.[11]

In decision analysis studies, prophylactic colony stimulating factors, as filgrastim, demonstrated a high cost-effective strategy, significantly reducing neutropenia occurrence and consequent hospitalization, lowering health both direct and total costs; this strategy is is highly cost-effective when the risk of hospitalization due to febrile neutropenia is more than 20% (Figure 4).[3]

According to the *National Cancer Center Network* guidelines, prophylactic administration of filgrastim or pegfilgrastim should take place when the risk of infection during first cycle of chemotherapy is >20% and in patients aged >65 years during chemotherapy regimen dose intensity comparable to CHOP.

In the end, many studies showed that anaemia is an independent risk factor for bone marrow toxicity, due increased free drug amount in circulation during anaemia; thus, it is important to maintain hemoglobin level over 12 g/dL in this patients population.

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Rational cytokine design holds the key to enhanced biological activity

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Polyethylene glycol (PEG) is a non-toxic, water-soluble neutral polymer approved by FDA (Food and Drug Administration) for human use in January 2002. PEG is covalently bound to an amino acid residue of proteins, in order to obtain a molecule with both a hydrophobic chain, the protein, and an hydrophilic moiety, PEG. Peculiar biochemical structure of PEG-conjugation explains its advantages over an unconjugated protein. First of all, PEG conjugation increases the solubility of hydrophobic proteins in aqueous solvents and improves their chemical stability; thus, the distribution volume and unabsorbed amount of protein at the site of inoculum are both reduced. Conjugation also allows both the reduction of protein renal clearance, which is usually high for proteins with molecular weight below 12 kDa, and proteolytic degradation. Plasma half-life is increased from 4 to 400 folds as compared to unconjugated protein. Increased absorption and plasma half-life allows the reduction of total protein dose required for therapeutic effect. Another advantage is the reduction of nonspecific intracellular penetration and nonspecific interaction with other proteins or cells, including immune cells; therefore, immunogenicity as well as adverse reactions are both reduced. In vitro experimental models provided evidence that PEG conjugation with poly-L-lysine micro-spheres markedly reduced non-specific interactions between peptides and cellular membranes, limiting phagocytosis of micro-spheres by macrophages and dendritic cells.[1] Because of the potential improvements in biologic profile of therapeutic proteins, granulocyte-colony stimulating factor (G-CSF, filgrastim) was conjugated to PEG in order to obtain pegfilgrastim. Development of pegfilgrastim focused on the evaluation of the differences in the pharmacokinetic and pharmacodynamic profiles as compared to filgrastim. The biological effect of the two molecules was studied in normal and neutropenic murine animal model: a single dose of pegfilgrastim 1 mg/kg subcutaneously (s.c.) or four doses of filgrastim 125 µg/kg s.c. were administered and the effect on bone marrow was assessed. Proliferative stimulation on bone marrow cells was superior with pegfilgrastim than with filgrastim: with respect to myeloblasts and promyelocytes, the labeling index of bone marrow cells in animals treated with filgrastim (56.5%) was similar to control animals (55.5%) but it was markedly increased in animals treated with pegfilgrastim, both normal (75.2%) and neutropenic (76.8%). Moreover, the duration of cell cycle was reduced in bone marrow cells: 9.1 hours in controls, 7.6 hours in normal animals treated with filgrastrim, 6.6 and 6.5 hours in normal and neutropenic animals, respectively, receiving pegfilgrastim. The superior efficacy of PEG-conjugated cytokine was even more evident on myelocyte proliferation; indeed, the labeling index and cell cycle duration of normal animals given filgrastim (29.4% and 16.2 hours, respectively) and pegfilgrastim (51.1% and 9.8 hours, respectively) was considerably different.[2] Maximum neutrophil count after cytokine challenge was also evaluated and showed a marked increase with pegfilgrastim ($1.8x10^9$/L in controls, $15.5x10^9$/L in non-neutropenic animals and $24.0x10^9$/L in neutropenic animals) and filgrastim ($1.8x10^9$/L in controls, $25.7x10^9$/L in non-neutropenic animals and $18.0x10^9$/L in neutropenic animals). Moreover, with both growth factors, the time of peak appearance of neutrophils in peripheral blood was reduced from 3.4 days to 1 day; neutrophil half-life in peripheral blood and cellular amplification factors were also increased (Figure 1).[2] Kinetic studies in humans given a single dose of pegfilgrastim, confirmed the data obtained in animal models and showed a rapid neutrophil release in peripheral blood within few days.[3] Filgrastim is a protein with molecular weight of 18.8 kDa obtained by heterologous expression in *Escherichia coli* transduced with a plasmid vector containing the human G-CSF gene. Filgrastim and pegfil-

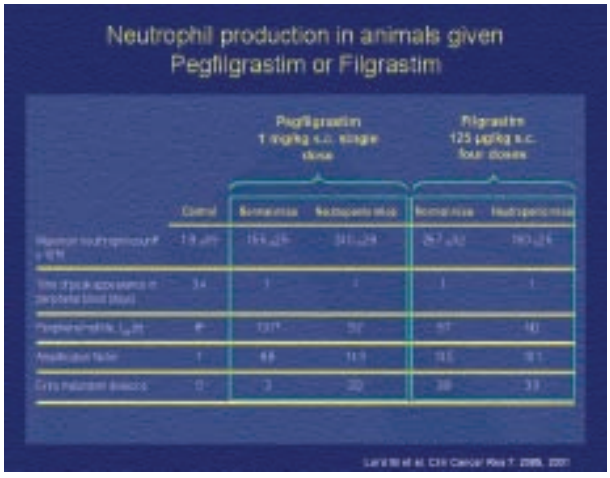

Figure 1. Effect of pegfilgrastim and filgrastim on neutrophil production in animals.

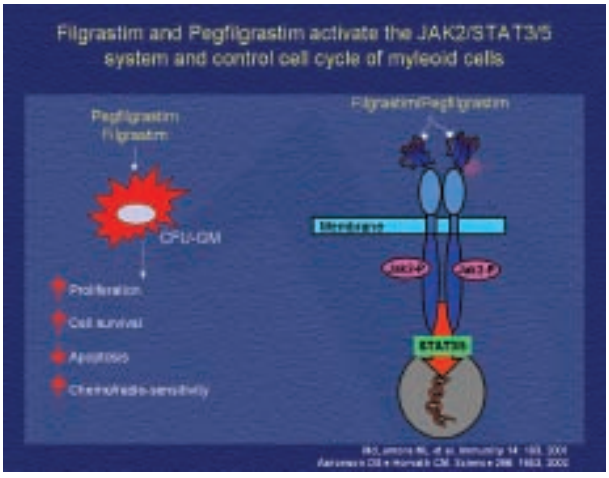

Figure 2. Cellular effects and signal transduction pathway of filgrastim and pegfilgrastim in myeloid cells.

grastim bind to a specific receptor (G-CSFR) expressed on the cell surface of haematopoietic cells and stimulate several cellular functions such as proliferation, differentiation, chemotaxis, phagocytosis, cytotoxicity and antigen response. Intracellular signal transduction after cytokine binding to G-CSFR is the same for pegfilgrastim and filgrastim: both of them activate the JAK2/STAT3/5 system, by which they control cell cycle of myeloid cells, via transcriptional activation of cell-cycle related genes (Figure 2). Both of them act on CFU-GM (granulocyte/macrophage colony forming units), thereby increasing cellular proliferation, extending survival and reducing apoptosis. Receptor binding specificity of pegfilgrastim is enhanced with respect to filgrastim due to PEG conjugation, which reduces non-specific binding of protein to non-myeloid cells.[4,5] From a pharmacokinetic point of view, the two compounds have different profiles, mainly regarding half-life. A study in healthy volunteers, comparing the administration of a single dose of filgrastim 5 µg/kg or pegfilgrastim 60 µg/kg, showed that they both reached maximum peak concentration within 1-2 hours post-dose; filgrastim concentrations decreased very rapidly, while pegfilgrastim levels remained high during time, with a slower decrement and a persistence in circulation for up to 2 weeks.[3] In a randomised trial on cancer patients treated with myelotoxic chemotherapy, filgrastim and pegfilgrastim pharmacokinetics were compared after multiple administration schedules: 1) filgrastim 5 µg/kg on days 1-5 before chemotherapy (cycle 0) and from day 3 after chemotherapy to neutrophil recovery ($10x10^9$ cells/L); 2) single dose of pegfilgrastim 30 µg/kg, 100 µg/kg and 300 µg/kg on day 1 of cycle 0 and day 3 post-chemotherapy. Study results showed that peak concentration of pegfilgrastim increased non-proportionally with the dose and detectable concentrations of the cytokine were observed up to 14 days after administration. Moreover, serum concentrations before chemotherapy plateaued for approximately 2-3 days, while, after chemotherapy, the duration of *plateau* increased to 7 days.[6] Concerning single pharmacokinetic parameters, both before and after chemotherapy, pegfilgrastim showed higher values of half-life and area under the concentration-time curve (AUC) than filgrastim. Moreover, pegfilgrastim presented a non-linear pharmacokinetics, as evidenced by the reduction in apparent clearance and non-proportional increase in AUC with respect to the dose administered. The observed differences in pre- and post-chemotherapy AUC values of pegfilgrastim 300 µg/kg (56,600 and 137,000 ng/mlxh, respectively), were dependent on neutropenia which reduces the cell-dependent clearance of the cytokine and increases peripheral tissue exposure, particularly bone marrow (Figure 3).[6] Johnston *et al.* also compared different administration schedules of filgrastim and pegfilgrastim on absolute neutrophil count.6 Before chemotherapy, pegfilgastrim administration produced a dose-dependent increase in absolute neutrophil count that lasted up to 12 days. The neutropenia induced by the administration of cytotoxic chemotherapy with paclitaxel and carboplatin was more severe and of longer duration in patients given daily doses of filgrastim 5 µg/kg and a single dose of pegfilgrastim 30 µg/kg, than in patients treated with pegfilgrastim 100 and 300 µg/kg.[6] Pegfilgrastim pharmacokinetics shows a clear dependence on neutrophil count; indeed, in a study on patients treated with docetaxel and doxorubicin in which pegfilgrastim 6 mg was administered post-chemotherapy, the plateau phase of cytokine levels was reached during absolute neutropenia because of the decrease in

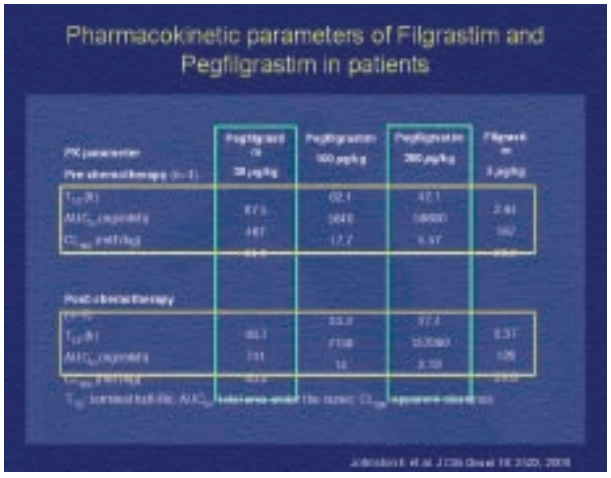

Figure 3. Parameters of filgrastim and pegfilgrastim distribution and clearance in cancer patients.

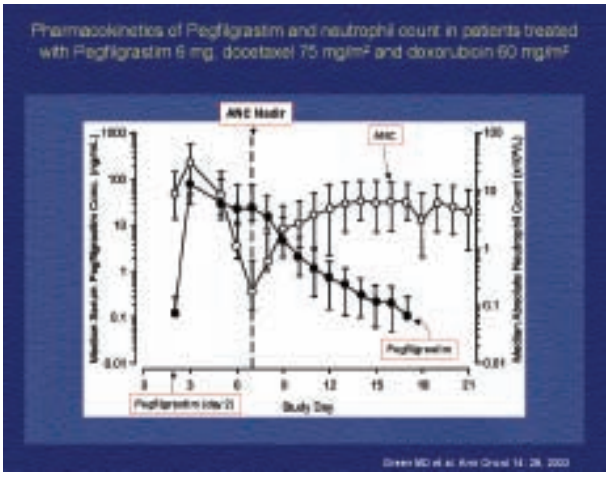

Figure 4. Pharmacokinetic (serum concentrations) and pharmacodynamic profile (neutrophil count) of pegfilgrastim in patients treated with docetaxel and doxorubicin.

cells expressing G-CSFR. This in turn results in high drug concentrations that will exert a potent stimulatory effect on bone marrow cells. Serum concentration of pegfilgrastim then progressively decreased during the phase of neutrophil recovery (Figure 4).7 Pharmacokinetic differences between filgrastim and pegfilgrastim are explained by the process of cytokine elimination from the body; indeed, pegfilgrastim clearance is almost exclusively dependent on G-CSFR binding and internalization leading to intracellular proteolysis and it is regulated by the number of neutrophils. Renal filtration and liver proteolysis with biliary excretion are both important for filgrastim but are of marginal importance for pegfilgrastim because conjugation with PEG increases the molecular weight of the molecule and prevents both renal filtration and liver uptake. Based on the results published in the literature, half-life of pegfilgrastim is 8-25 times longer than filgrastim and its pharmacokinetic profile is non-linear, because of the lack of renal and hepatic clearance and of its removal from the circulation by endocytosis mechanisms. In conclusion, pegfilgrastim represents a new formulation of filgrastim characterized by extended half-life, high tissue exposure, and sustained proliferative response by bone marrow cells. From a pharmacodynamic point of view, a single administration of pegfilgrastim produces the same biologic effect of multiple administrations of filgrastim. The availability of a single dose schedule for pegfilgrastim offers the possibility of a considerable simplification of the management of chemotherapy-induced neutropenia and improves the quality of life of patients.

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From laboratory to clinics: fixed dose, once-per-chemotherapy-cycle pegfilgrastim for prophylaxis of neutropenia in patients with cancer

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Febrile neutropenia (FN) has termed a condition in which severe neutropenia (absolute neutrophil count <0.5x10^9/L) is associated with fever. The risk of FN is directly related to severity and duration of the neutropenia and it also represents a life-threatening complication of chemotherapy: serious infections generally require intravenous antibiotic treatment and a prolongation of length hospitalisation.[1,2] Despite immediate hospital admission and a correct antibiotic treatment, mortality related to infections is very high, up to 7% of cases.

Neutropenia is a major dose-limiting toxicity of chemotherapy which could delay chemotherapy administration, thus compromising therapeutic success;[1,3,4] moreover, neutropenia has an additional impact on economic costs, quality of life and social-familiar aspects.[1,2,5] Despite these issues, an average less than 10% of patients under chemotherapy treatment receives a prophylaxis for neutropenia.

In a USA Study, on patients treated with chemotherapy for early-stage breast cancer, chemotherapy dose delay or dose reduction occurred in about half of patients (45%) and 30% of cases required a reduction of dose intensity (RDI) < 85% of planned regimen; only 17% of patients received growth factor.[6]

From literature data, neutropenia incidence varied widely on the basis of different standard chemotherapy regimens: 8% to 51% with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) for Non Hodgkin's Lymphoma (LNH), 1% to 78% with CMF (cyclophosphamide, methotrexate, fluorouracil) for breast cancer and 3% to100% with CAF (cyclophosphamide, doxorubicin, fluorouracil) or FEC (fluorouracil, epirubicin, cyclophosphamide).[1] Consequently, even if myelotoxicity is a clear side effect of chemotherapy, so far it's not possible to assign a specific risk factor to many commonly used regimens.

The reported incidence of neutropenia event and of its complications has a broad range: 2% to 28% for severe neutropenia, 10% to 57% for febrile neutropenia, 0% to 16% for severe infections, 0% to 7% for death due to febrile neutropenia.[7] Hospitalisation for febrile neutropenia has a mean length stay of 11 days (median 6 days), and this fact produces a remarkable impact on economic costs.[8]

Phase I/II Studies, of growth factors G-CSF (filgrastim) and its PEG-conjugated compound (pegfilgrastim), showed efficacy of growth factors relative to neutrophil count recovery[9] and to consequent reduction of neutropenia and its complications incidence.

The UK *Neutropenia Audit* studied 422 patients with primary breast cancer under adjuvant chemotherapy (61% treated with a CMF like regimen and 39% with anthracycline based regimens), showed a neutropaenic events occurrence in 29% of cases, a reduction of dose intensity (ID) <85% of planned dose in 17% of cases (due to chemotherapy-induced neutropenia in 11% of cases) and, finally, a prophylaxis with G-CSF only in 5.2% of patients. Relatively to CMF regimen, ID reduction occurred in 95.7% of patients without neutropenic event and in 86.9% of patients with neutropenic event; relatively to anthracyclines rates were respectively 96.3% and 87.4%.[10]

Delivering chemotherapy sub-optimal doses, reduces the chance of relapse-free survival, with an proportional effect based on used doses; the delivered dose should be >85% of optimal dose in order to have a significant effect on survival.[11]

CALGB 9741 Trial is a recent important study, comparing the effect of sequential or concurrent TAC regimen (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 and paclitaxel 175 mg/m^2) with a 2 week (Q2W) or 3 week (Q3W) schedule, as adjuvant chemotherapy in breast cancer patients; in Q2W schedules primary prophylaxis with filgrastim was administered on the basis of an expected 40% neutropenia incidence. Patients could be enrolled if they have node positive breast cancer without evidence of

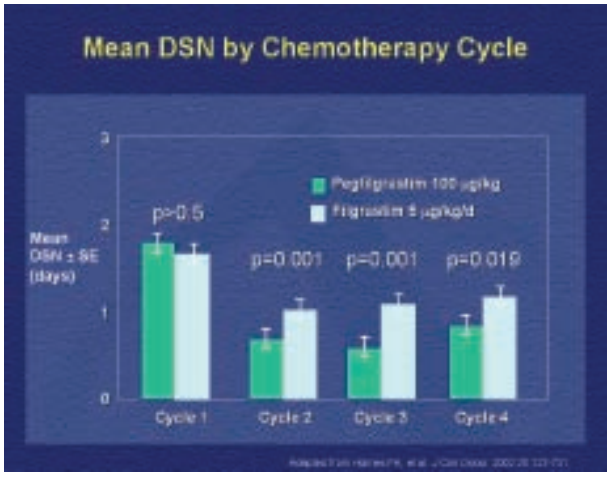

Figure 1. Mean DSN by chemotherapy cycle.

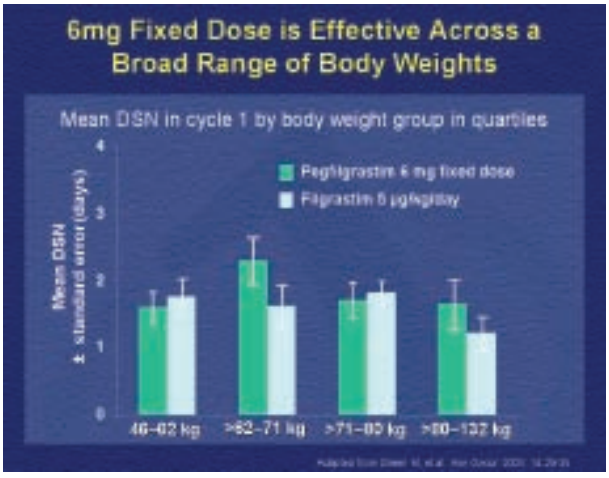

Figure 2. Fixed dose is effective across a broad range of body weights.

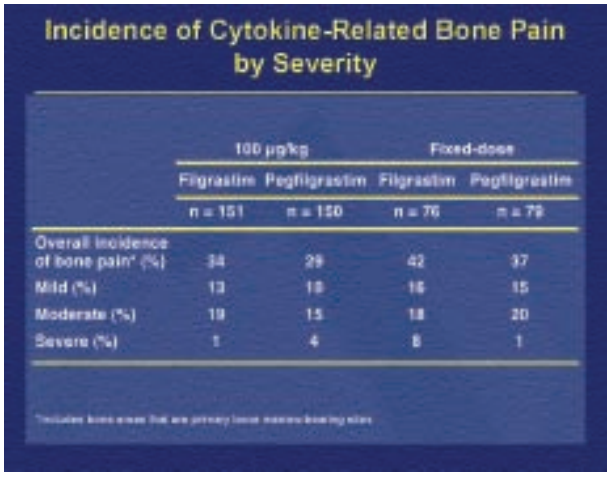

Figure 3. Incidence of cytokine-related bone pain by severity.

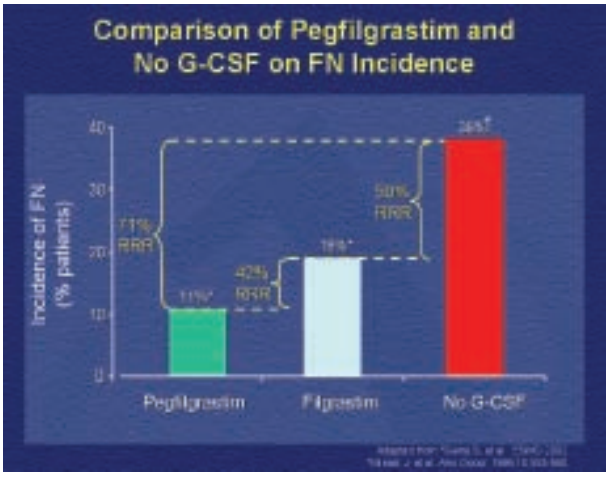

Figure 4. Comparison of pegfilgrastim and No G-CSF on FN incidence.

distant metastasis (Stage T1-3, N1-2, M0), they had primary surgery with lumpectomy associated with axillary dissection or modified radical mastectomy (MRM) with clear margins; blood and other examinations required a minimum absolute neutrophil count of 1,000 cell/µL, minimum platelets of 100,000/µL, normal bilirubin, normal chest X-ray and ECG. The 4-years analysis showed that disease-free survival was significantly better with Q2W regimens than Q3W regimens (82% versus 75%, respectively; p=0.00014). Moreover, hospitalisation rate due to febrile neutropenia was actually lower in 2 weekly than 3 weekly arms (2% in sequential and concurrent Q2W regimens versus 3% in sequential Q3W versus 5% in concurrent Q3W regimen); these data probably reflect the use of primary prophylaxis with filgrastim in 2 weekly regimens, in opposition to secondary prophylaxis of 3 weekly regimens. A higher incidence of side effects was observed in concurrent than sequential regimens.[12]

Several studies demonstrated differences between filgrastim and pegfilgrastim, consisting of the same filgrastim core (molecular weight of 18.7 kd) with a PEG molecule (20 kd) attached covalently to the N terminus, resulting in a molecule with doubled molecular weight. While filgrastim is characterised by a plasmatic half-life of 3 hours, thus requiring daily injections, longer half-life of its pegylated formulation produces sustained plasmatic concentrations and makes once-per-chemotherapy-cycle dosing possible.[13] Clearance of pegfilgrastim depends on neutrophil concentration, with a self-regulation mechanism: it remains in serum for prolonged period of time during neutropenia condition; it is cleared as neutrophil are stimulated to return to normal by pegfilgrastim and their

count rises.[14] Tolerability of pegfilgrastim is similar to that of filgrastim.[9,14,15]

Simple fixed dose of pegfilgrastim offers advantages to patients and to healthcare professionals, eliminating potential risk of erroneous doses. Consequently several studies had been conducted comparing the two formulations.

Data are available from two Pilot Phase III Studies in patients with breast cancer receiving chemotherapy treatment with doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) randomised to treatment with pegfilgrastim (single injection of 100 µg/kg in the study conducted by Holmes *et al.*, or a 6 mg fixed dose in the study conducted by Green *et al.*) or with daily filgrastim (5 µg/kg as standard protocol). Eligibility criteria for study entry were as follows: high risk, stage II-IV breast cancer; woman >18 years old; performance status >2; no prior chemotherapy, with the exception of adjuvant therapy o metastatic regimen; white cells >4x10^9/L, platelets >150,000x10^9/L; adequate renal, hepatic and cardiac function; no radiotherapy within 4 weeks, non bone marrow transplantation o peripheral blood stem cells transplantation. In the study conducted by Holmes et al. the average duration of severe neutropenia was 1.7 days in pegfilgrastim (100 µg/kg) arm and 1.8 days in filgrastim arm; in the second study it was 1.8 days in pegfilgrastim (6 mg) arm and 1.6 days in filgrastim arm.[14,16] Both filgrastim and pegfilgrastim produced a similar increase in absolute neutrophil count. Moreover, pegfilgrastim was high effective with respect to reduction of severe neutropenia duration across all subsequent chemotherapy cycles, during which its effect was superior than that obtained in the first cycle and superior than the effect reached by filgrastim (Figure 1).[14] In the Phase III randomised trial, comparing fixed-dose of pegfilgrastim (6 mg) and filgrastim, no correlation between body weight and efficacy was observed in patient treated with pegylated formulation across all chemotherapy cycles (Figure 2).[16] In both studies, pegfilgrastim demonstrated a higher efficacy in reducing overall rates of febrile neutropenia events when compared with filgrastim; this difference was statistically significant if considering body weight based dosing (9% versus 18% respectively; p<0.05), but was observed with fixed dose formulation (13% versus 20%) too, even if not statistically significant due to small numerous of patients.[14,16] A commonly reported side effect of filgrastim is the occurrence of bone pain.

Safety profile of pegfilgrastim is similar to filgrastim, as showed in the two randomized trials (Figure 3). Based on data from the two pilot studies, thus fixed dose once-per-chemotherapy-cycle pegfilgrastim, presents the same efficacy and safety of daily filgrastim administration and reduces febrile neutropenia incidence, mainly if considering body weight based dosing. Due to identical enrollment criteria in in the two studies, a combined analysis had been performed, in order to evaluate efficacy relative to a more numerous group; the incidence of febrile neutropenia was 11% in patients treated with once-per-cycle administration of pegfilgrastim and 19% in patients with daily administration of filgrastim, with a statistically significant difference (p <0.05).[15] The use of filgrastim reduced the relative risk of febrile neutropenia of about 50% if compared with no use of cytokines during chemotherapy; pegfilgrastim allowed a further reduction of 42% if compared with no-pegylated formulation and a consequent relative 71% overall reduction in febrile neutropenia compared with no treatment (Figure 4). Finally, patients treated with pegfilgrastim had a lower risk of anti-infective use compared with filgrastim (19% versus 21%; RR 0.89, 95% CI 0.60,1.32).

The rationale for using once-per-cycle pegfilgrastim is its similar efficacy when compared with filgrastim, in terms of reduction of severe neutropenia duration and of FN incidence, in addition to its similar safety profile, the protective *self-regulation* mechanism based on neutrophil count, the superior convenience of a single injection. 6 mg fixed doses is as effective as weight based dosing.

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Dose-dense chemotherapy for non-Hodgkin's lymphoma

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First data concerning efficacy of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) protocol in the treatment of aggressive non Hodgkin's lymphomas (LNH), demonstrated that survival rate after 24-36 months varied based on their aggressivity: it was better with diffuse poor lymphomas (80%) and worse with diffuse mixed forms (50%).[1] Following studies showed that new generation chemotherapy regimens, such as m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, desametasone), ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, prednisone, cytosine arabinoside, bleomycin, vincristine, methotrexate and calcium leucovorin), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) didn't produce a better disease-free survival than CHOP: 3-years survival estimate of event-free survival was 48%, 46%, 41%, and 41% (p=0.35) with respectively four regimens.[2]

Considering survival, risk factors and age of patients are clearly more important factors than used regimens. According to International Prognostic Index (IPI) patients can be classified in 4 risk groups (low, low-intermediate, high-intermediate and high) based on the presence of respectively 0, 1, 2 e 3 risk factors. Besides, survival data are influenced by patient age. For patients <65 aged 5-years survival rates are 83% if in low risk group and 32% if in high risk group, while for elderly patients (>65 years) these rate decrease to 56% and 21%, respectively in low and high risk classes.

Therefore, the *Deutsche High Grade Non Hodgkin's Lymphoma Study Group* (DSHNHL) individualized 3 treatment patients groups in which performing different clinical trials: elderly patients (>60 years) (NHL-B-2), young patient with low risk (IPI 0-1) (NHL-B-1) and young patients with high risk (IPI >2) (NHL-A).

The introduction of granulocyte-colony stimulating factor (G-CSF) in clinical practice, made possible for increasing dose intensity up to 25% and reducing time between administrations (densification) up 50% in the lymphoma management, compared with previous standard regimens. Maybe a strategy based on the combination of dose intensification and dose densification could produce an additional effect. For NHL B1 and B2 patients, several intensification and densification cycles schedules of CHOP have been formulated: standard CHOP, delivered every 21 (CHOP-21) or 14 (CHOP-14) days; CHOEP regimen (CHOP with the addition of etoposide) every 21 days (CHOEP-21) or 14 days (CHOEP-14); in two weekly regimens G-CSF is administrated on days 4-12 (Figure 1).

Relatively to younger low risk patients (NHL-B-1), DSHNHL conducted a clinical trial with 2x2 factorial design, comparing 4 chemotherapy regimens (CHOP-21, CHOEP-21, CHOP-14, CHOEP-14) for a total of 6 cycles. From September 1994 to June 2000, a total of 866 patients were enrolled, 762 of whom eligible and valuable for analysis. Median age was 48 years; patients had IPI-0 in 67% of cases (30% IPI-1 and 3% IPI-2), increased values of LDH in 0% of cases, disease stage III-IV in 31%, ECOG performance status >1 in 6%, extranodal disease >1 in 15%, B symptoms in 22%, Bulky disease (extension >7.5 cm) in 28% of cases. An administration of median >95% of planned dose had been possible across all cycles.

After a median observation of 58 months, study results showed the therapeutic advantage with etoposide addition to CHOP regimen with respect to efficacy, while administrations frequency didn't have a significant effect. With respect to etoposide addition, complete remission (CR) rates were 89,8% with CHOEP-21/CHOEP-14 regimens and 84,2% with CHOP-21/CHOP-14 regimens (p=0.02); considering the effect of time interval, CR was observed in 85.9% of case treated with 3 weekly CHOP-21/CHOEP-21 and in 88.3% of cases treated with 2 weekly CHOP-14/CHOEP-14 (p = 0.3). Time interval showed no effect (p=0.313 for comparing 2 weekly and 3

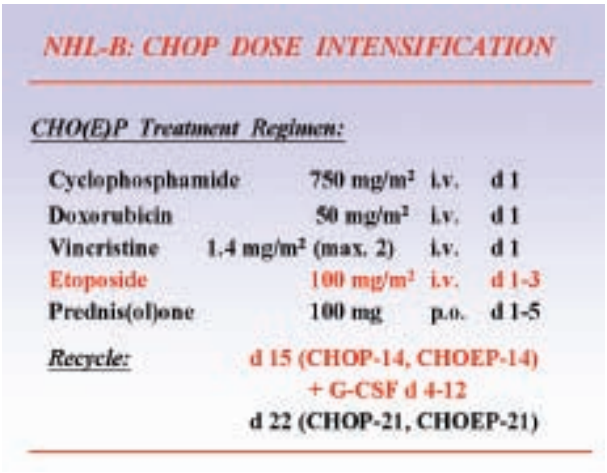

Figure 1. NHL-B: CHOP dose intensification.

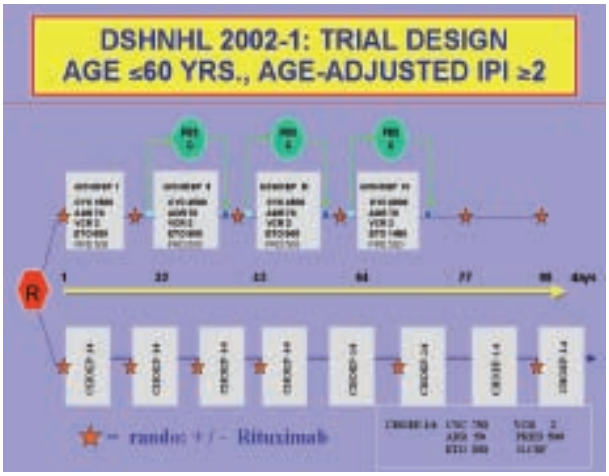

Figure 2. DSHNHL 2002-1: trial design.

weekly regimens) while addition of etoposide showed a significant effect (72% with regimens plus etoposide versus 62% with regimen without etoposide; p=0.0104) on 5-years disease-free survival. Nevertheless, both addition of etoposide and time interval reduction, did not significantly affect overall survival in this patients group (p=0.1890 for addition of etoposide, p=0.1350 for reduction of time interval). If considering only young patients with one IPI, after age-adjustment, the addition of etoposide produced a significant improvement of both 5-years events-free survival (from 46% with CHOP-14/CHOP-21 regimens to 70% with CHOEP-14/CHOEP-21) (p=0.0009) and overall survival (from 72% to 85%, respectively; p=0.0097). In this patients category, CHOEP-14 showed a better event-free survival (RR=0.661, p=0.021) and overall survival (RR=0.612; p=0.04) risk relative compared with CHOP-21. The effect of 3 weekly administration of CHOEP was not so significant compared with CHOP-21: RR=0.643 for event-free survival (p=0.014) and RR= 0.720 (p=0.15) for overall survival. Thus, CHOEP could be considered as the first improvement strategy after CHOP introduction. As showed by study results, addition of etoposide to CHOP in young low-risk LNH patients could be a good strategy in terms of complete remission and events-free survival rates; in patients with IPI=1 such benefit was evident even considering overall survival. CHOEP could be considered the first choice treatment strategy in young patient with aggressive LNH.

A relevant question that need to be resolved is the role of rituximab in association with CHOP-like regimens in young low-risk patients.

With reference to high-risk young patients group (NHL-A) a diffuse debate still exists in scientific community. In this subpopulation CHOP-21 is formally the standard treatment and so far alternative approaches, as CHOEP or addition of rituximab, hadn't been tested. Novel approaches are thus needed. With reference to this, DSHNHL developed a clinical trial in order to evaluate a new treatment regimen, the mega-CHOEP, in which the most efficacious drugs for lymphoma treatment, as CHOP and etoposide, in addition to increasing dosing will be tested. Four cycles of mega-CHOEP (increase in dosing on second and fourth cycles) will be compared to 8 cycles of CHOEP-14; both treatment could be associated with rituximab, in a randomised manner (Figure 2). The present trial is still ongoing and results are not available so far.

For the treatment of patients with NHL and over 60 years of age (NHL-B-2), a DSHNHL trial compared 4 different regimens (CHOP-21, CHOEP-21, CHOP-14, CHOEP-14) administered for a total of 6 cycles. In this clinical trial, from September 1994 to June 2000, a total of 831 patients were enrolled, 738 of which eligible and valuable for analysis; the median observation time was 58 months. Patients had a median age of 67 years, 0 IPI in 40% of cases (1 in 36%, 2 in 18%, 3 in 6%), LDH level above normal value in 46%, stage III-IV in 51%, ECOG performance status >1 in 19%, extra-nodal disease >1 in 25%, B symptoms in 37%, Bulky disease in 39%. Unlike young patients, elderly patients treated with CHOEP-14 regimen, a high reduction of relative dose of chemotherapy was observed (86% for cyclophosphamide, 85% for doxorubicin, 84% for etoposide). Relatively to efficcay data, complete remission rates were 14% superior with CHOP-14 compared with CHOP-21 regimen (77.1% versus 63.5%, p=0.005). On the basis of LDH baseline value, the superior effect of CHOP-14 compared with CHOP-21, was markedly observed in patients with high levels of LDH: CR respectively 68.3% and 44.1% (Figure 3). CHOP-14

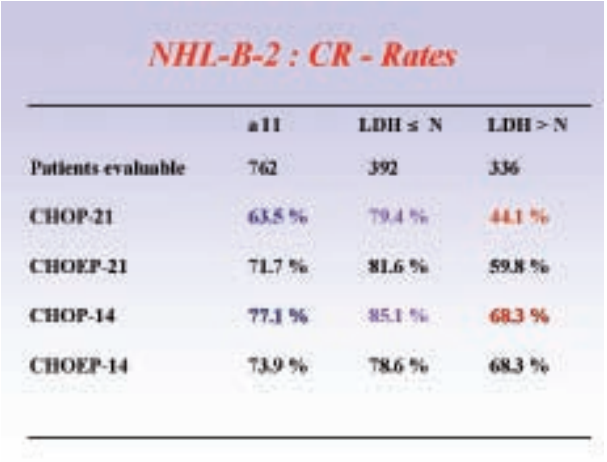

Figure 3. NHL-B-2: CR rates.

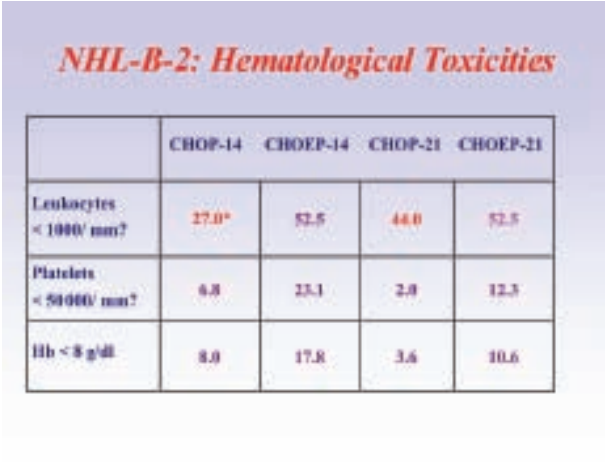

Figure 4. NHL-B-2: hematological toxicities.

regimen produced a better survival free from therapeutic failure both after 3 years (56% versus 41%) and 5 years (43% versus 32%) compared to CHOP-21; this beneficial result was observed even on overall survival after 3 years (70% versus 48%) and 5 years (52% versus 39%). Minor effect on 5 year-survival could be influenced by advanced patients age, which represents an intrinsic risk factor for increased mortality. With reference to haematological toxicity, with G-CSF administration during 2 weekly regimens, leucopoenia (leukocytes <1000/mm^3) was observed less in CHOP-14 regimens (27%) than in CHOP-21 (44%) regimens (Figure 4).

In conclusion, in elderly patients CHOP-14 regimen showed better efficacy than CHOP-21 regimen and, thus, it should be considered new reference and standard regimen for this population.

The *Japan Clinical Oncology Group* conducted a phase III randomised trial comparing standard CHOP regimen with bi-weekly CHOP in patients with aggressive LNH without stratification according patients age; study results were discordant from those of the study described above: no difference was observed between the two treatment regimens with reference to overall survival (RR=1.06; 95% CI: 0.66-1.70).[3] Discordance could be explained mainly by reduction of doses of CHOP-14 in a high percentage of patients: <90% dosing in 27% of cases and <80 in 20%; a dosing reduction < 90% and <80% was present in a minor proportion of patients both in NHL-B-1 trial (9% and 2% respectively) and in NHL-B-2 trial (11% and 10% respectively).

The *French GELA 98.5 Study* tested a novel approach in LNH treatment, in which rituximab was added to CHOP-21 regimen; this association showed a significant increase of 3-years overall survival (p=0.007).

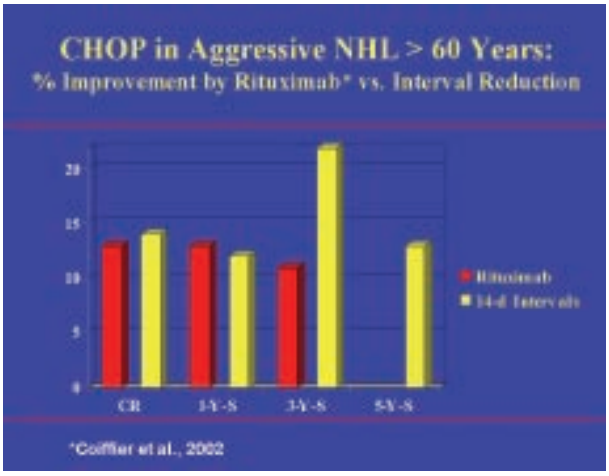

Figure 5. CHOP in aggressive NHL in patients 60 years older.

When compared to the strategy of reducing time interval to 14 days, rituximab seems to have a similar efficacy in terms of complete remission and 1-year survival, but considering 3 years survival efficacy of rituximab seems clearly inferior (Figure 5).[4] CHOP-14 could be considered better than CHOP-21 in elderly patients. Even the addition of rituximab showed more beneficial effect than standard CHOP-21, but is a strategy too expensive; long term data show better efficacy of CHOP-14 when compared to the association CHOP-21+rituximab. On the basis of these considerations, CHOP-14 could be considered as the new standard regimen for this patients population.

Finally, DSHNHL tested the efficacy of association of CHOP-14 and rituximab, in a clinical trial (RICOVER-60) in which patients with 61-80 years were randomised in 4 treatment arm: 6 cycles of CHOP-14, 8

cycles of CHOP-14, associated or nor with 8 cycles of rituximab. Specific measures for elderly patients were adopted in the study: a pre-phase therapy with vincristine and prednisolone for a week; evaluation of eligibility only after pre-phase; organ toxicity control after 4 cycles; hydrocortisone substitution in case of fatigue. From July 2000 to March 2003, 890 patients were enrolled, 437 of which evaluable for interim analysis, with a median time of observation of 16 months. Differences between NHL-B-2 trial and RICOVER-60 trial were evaluated. Unlike NHL-B-2 trial in which G-CSF was administered for 10 days (d4-d13), in this trial administration started two day after (d6-d12) for an total duration of 7 days. This resulted in an increased rate of grade 3 and 4 infections (5.2% vs. 2.4%). Therefore, an amendment was made, and all patients in the RICOVER trial now receive 10 days of filgrastim. Interim analysis data, showed a failure-free survival of 60% and an overall survival of 78% after 25 months. All treatment arms of this study appear feasible, safe and effective. The study, is still opened planning to enrol a total of 1,280 patients, in order to evaluate the efficacy of rituximab.

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Clinical evidence for pegfilgrastim: current status and future applications

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In clinical practice potential indication for pegfilgrastim use are the following: neutropenia induced by chemotherapy, stem cells collection, recovery phase after bone marrow transplantation and dose-dense chemotherapy regimens (Figure 1).

Risk factors for the occurrence of neutropenia are numerous: advanced age (>70 years) represents a predictive factors both of febrile neutropenia (FN) and of increased haematological toxicity. A meta-analysis of studies conducted in Non Hodgkin's lymphoma (LNH) patients treated with CHOP or CHOP-like regimens, showed that incidence of neutropenia in elderly patients varied among different studies, reaching a value of about 50% in some studies.[1] A high-tumour burden could cause neutropenia mainly during first chemotherapy cycle; hence the choice of primary or secondary prophylaxis strategy with growth factors is crucial. Mortality studies in elderly patients (>60 years) during chemotherapy for aggressive LNH two third of deaths occurred in the first chemotherapy cycle and that in 83% of cases death was related to infections (presence of absolute neutrophil count <500/mm^3 in 66% of cases).[2] Bone marrow infiltration is commonly observed in some malignancies, such as LNH, breast cancer, small cells lung cancer (SCLC); it represents a further risk factor for neutropenia. Lymphocytopenia severity could influence the occurrence of neutropenia, even if not many studies evaluated this correlation. A study conducted by Blay *et al.*, evaluating the correlation between lymphocytopenia value on day 1 and on day 5 of chemotherapy showed that the incidence of febrile neutropenia was significantly related to lymphocytes count on day 5 of chemotherapy (Figure 2).[5] Initial performance status (PS) of patient is a relevant risk factor, independently off the age: incidence of febrile neutropenia was 9% in patients with initial PS 0-1 and 14% in patients with PS>1 (p=0.03).[5] A previous febrile neutropenia event increases the risk of a consequent new event by about 6 folds: the incidence was 4.7% and 29%, respectively in patients with no or previous event (p=0.005). Other risk factors are previous exposition to chemotherapic or radiotherapic agents, use of regimens with drugs with high haematological toxicity. Regimens exposing to high risk of neutropenia are those containing doxorubicin (>75 mg/m^2), epirubicin (>90 mg/m^2), cisplatin (>100 mg/m^2), etoposide (>500 mg/m^2), cytarabine, (>1 g/m^2), ifosfamide (>6 g/m^2) and cyclophosphamide (>1 g/m^2).

G-CSF could be administered as primary prophylaxis to all patients, considering high cost-effective ratio, or alternatively as secondary prophylaxis only in patients with a febrile neutropenic event, reducing patients potential useless treated and increasing compliance. In clinical practice primary prophylaxis is commonly used with high-risk chemotherapy regimens or in presence of high-tumour burden, while secondary prophylaxis is preferred for low-risk chemotherapy regimens.

Two growth factors are now available, G-CSF (filgrastim) and its pegylated formulation (pegfilgrastim). Advantages of filgrastim are availability of selecting dose and duration of treatment, the adaptability to complex cycles, adjustable costs on the basis of use; on the contrary its administration requires a high compliance of patients due to multiple injections. Advantages of pegfilgrastim are its self-regulation mechanism, single injection per cycle, more simple administration; its important limitation is the fixed dose which does not allow the use in complex regimens, as BEP (bleomycin, etoposide, cisplatin) in testis tumour or in weekly regimens, as in breast cancer (Figure 3). Thus, the choice between the two formulation should be carefully made considering all factors relate to chemotherapy.

Pegfilgrastim use should be preferred in conditions of high risk of severe neutropenia, when date of nadir is unpredictable and the duration of neutropenia in unforeseeable, in conditions of high risk of severe

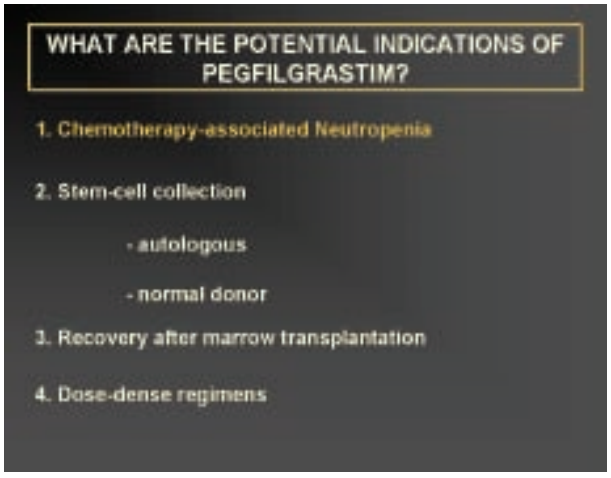

Figure 1. Potential indications of pegfilgrastim.

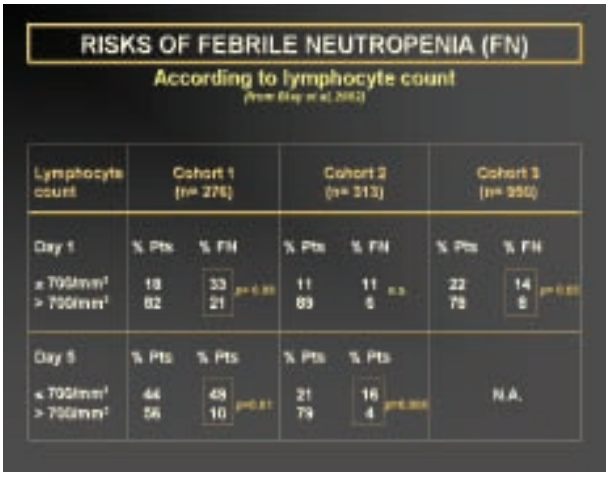

Figure 2. Risks of febrile neutropenia.

infections in presence of severe neutropenia (for example risk of sepsis, presence of underlying chronic obstructive pulmonary disease).

Another potential indication for pegfilgrastim is the stem cells collection, both autologous that from normal donors. In this context, clinical data are lacking. Studies are needed to evaluate if pegfilgrastim produces a higher number of $CD34^+$ cells and a longer duration of of $CD34^+$ cells in the blood compared with G-CSF, if it is effective in patients failing G-CSF treatment and if single injection is associated with lowered costs.

Potential advantages of pegfilgrastim in phases of recovery after stem cells transplantation could the self-regulation mechanism, particularly useful in this phase when neutropenia duration is unforeseeable, in addition to reduction of treatment costs and the possibility of outpatient treatment. There is no clinical trial comparing a single injection of pegfilgastrim between days 2 and 4 after transplantation with standard daily administration of G-CSF from day 5 to neutrophil recovery.

A further application field of pegfilgrastim is during *dense-dose* regimens. Dose-dense regimens are regimens in which higher doses of agents with demonstrated efficacy are administered with shorter delays between cycles in order to potenziate efficacy. Many data are avalilable in literature demonstrating the efficacy of *dose-dense*, such as CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisolone every 14 days), RICE (rituximab, ifosfamide, carboplatin, etoposide) in recurrence of lymphoma, weekly AC (adriamycin, cyclophosphamide) in breast cancer, administration of epirubicin every 14 days, dose-dense AT (adriamycin, docetaxel) o FEC (fluorouracil, epirubicin, cyclophosphamide), AC regimen every 14 days

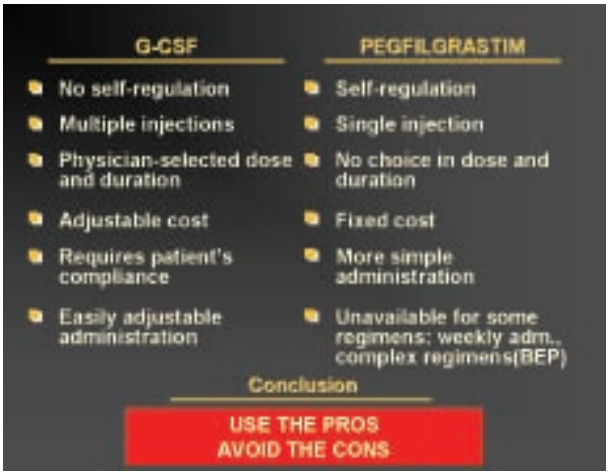

Figure 3. G-CSF versus pegfilgrastim.

associated with taxotere, CHOPR (CHOP+rituximab) every 14 days, BEACOPP (bleomicin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) every 14 days, ACE every 14 days.

Pegfilgrastim could be useful in the management of patients with chronic neutropenia, both in constitutional (cyclic and not-cyclic) or acquired (following myelodysplastic or lymphoprolipherative disorders or aplasia) forms. In these conditions, pegfilgrastim, due to its self-regulation mechanism, could reduce the frequency of injections, and improve quality of life. Clinical trials are needed; nowadays chronic neutropenia is not and indication for pegfilgrastim treatment.

The incidence of neutropenia is very high during radioimmunotherapy; the date of nadir, its duration and its severity is unforeseeable and neutropenia can

be severe in some cases. The characteristics of pegfilgrastim make it a potential good drug in this setting.

In antineoplastic treatment pegfilgrastim could be combined with monoclonal antibodies. The rationale is based on data relative to the combination of G-CSF with rituximab: G-CSF increased the expression of FcγRI receptors, the number of polymorphonuclear cells (PMN) and activated antibodies-dependent-cell-cytotoxicity of PMN. It has been demonstrated that receptor affinity for rituximab varies and depends on genetic expression of receptors with high or low affinity. *In vitro* studies showed that in patients with low sensibility to rituximab, the addition of G-CSF allowed a high affinity, by increasing the number of produced receptors or their activity. In a small trial of 19 patients with low-grade LNH, previously exposed to chemotherapy, *in vivo* administration of G-CSF (5 mg/kg/die for 3 days) in combination with rituximab (375 mg/m^2 on day 3) for 4 weekly cycles produced a doubled mean time to progression (24 months) even if overall response rate was not increased (42%).

Relatively to acute myeloid leukaemia (AML) some studies compared G-CSF and pegfilgrastim. In the randomised, double blind, Trial 20020153, once-per-cycle pegfilgrastim (6 mg) was compared with daily filgrastim, during 1-2 course of induction treatment (3 days of idarubycin and 7 days of cytarabine, IA3+7) followed by one course of consolidation (cytarabine at high doses, HiDAC).

With reference to use of pegfilgrastim during chemotherapy administration, safety and efficacy have not been evaluated yet; for this reason, pegfilgrastim should be administered 24 hours after chemotherapy. Clinical studies evaluating the concomitant administration in particular chemotherapy regimens, as CHOP, combination of carboplatin/taxol, and topotecan.

Both G-CSF and Peg-GCSF have showed to be useful in clinical practice even if for the latter formulation further studies are needed to address its use in particular clinical condition. In these new trials other parameters, as patient quality of life and pharmacokinetic analysis, should be added.

Based on efficacy data for both compounds and on different characteristics, the choice between them should be taken only considering all elements related to patients and to disease, in order to optimise their use.

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