Clinical and economic benefit of G-CSF administration in the prevention of chemo-induced neutropenia

Summary
Chemotherapy-induced neutropenia (CIN) is a frequent complication in cancer patients receiving myelosuppressive chemotherapy which can result in life-threatening infections requiring prolonged increasingly costly hospitalization. Furthermore, scheduled chemotherapy may be reduced or delayed as a result of CIN, which negatively affects prognosis. Granulocyte colony-stimulating factors (G-CSF) stimulate neutrophil production and maturation, and can therefore reduce the incidence and severity of neutropenia. A pegylated form of filgrastim, pegfilgrastim, has been developed, and various trials have shown that a single fixed dose (6 mg) per chemotherapy cycle is safe and effective in adult patients regardless of their body weight, thus making it a simple, effective, and well-tolerated option. This paper summarizes recent clinical data and analyses its place in the context of recent guidelines.

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Vito Lorusso
Direttore U.O. di Oncologia
Ospedale Vito Fazzi AUSL/LE
e-mail: vitolorusso@inwind.it

The introduction of growth factors in the early 1990s had - and continues to have - a deep impact on oncological practice. The numerous trials with these cytokines have allowed a lot of information to be gathered both on their biological effects and the indirect consequences of the decrease in neutropenia, anaemia and thrombocytopenia they provoke[1-3]. As specifically regards granulocyte colony-stimulating factors (G-CSF) and granulocyte macrophage colony stimulating factors (GM-CSF), our store of knowledge is still growing today: from the clinical point of view (benefits in terms of quality of life and mortality); from the physiopathological point of view (other neutrophil functions besides their barrier effect); and from the pharmacoeconomic point of view (cost-benefit ratio), thus making this category of drugs among the most versatile in oncohaematology[4,5]. This is confirmed by the frequent updating of the international guidelines that regulate the use of these drugs[6-8].

As regards the knowledge passed down to us on this group of molecules, it should be remembered that G-CSFs were principally used in the early 1990s in the treatment of chemo-induced neutropenia (or in patients with AIDS in antiretroviral therapy), whereas today they are used in the vast majority of cases as "proactive" drugs, i.e. in the primary and secondary prophylaxis of neutropenia, both with the aim of preventing the risk of infection and to allow planned chemotherapeutic action to

go ahead according to schedule[9-11]. In other words, granulocyte colony-stimulating factors have gone from being support drugs (*supportive care*) to being an integral part of the therapeutic plan themselves, since they allow the expected excellent results in terms of survival to be achieved[12-14]. *They therefore affect prognosis and the course of the disease directly*. In addition to this primary benefit, there is also an improvement in the quality of life[15-17].

In final analysis, in the light of the results of 15 years of large clinical trials and several meta-analyses, using G-CSFs means providing patients with a better prognosis and a better quality of life[18,19]. *There is also a non-negligible economic aspect since their use drastically decreases the costs of managing neoplastic patients, as we will see*[20,21].

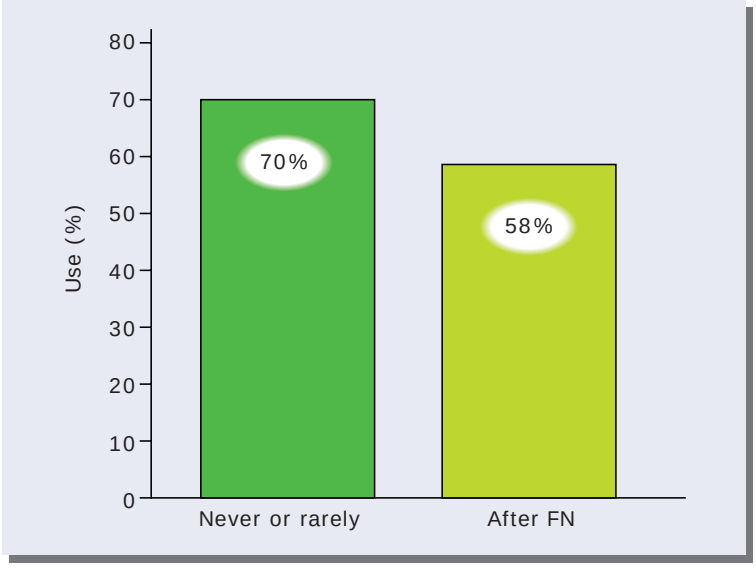
The Italian situation

At the end of 2006, the Associazione Italiana Oncologi Medici (AIOM, the Italian Association of Oncologists) issued guidelines regarding the use of erythropoietic and myelopoietic growth factors in prevention and treatment. This document followed a previous release in October 2003[22]. Similarly to documents issued by other international societies (EORTC, ASCUS and ESMO), it suggests filgrastim, pegfilgrastim and lenograstim prophylaxis right from a ?20% risk of neutropenia [6,22-25]. This indication is essentially the same as that found in the previous document. What are the repercussions of this on oncological practice? It is well known that several pharmacovigilance studies have systematically found that the guidelines have little effect on daily clinical practice[26,27].

The only existing survey in Italy was performed in the October 2003/January 2004 quarter by Danova et al. on a group of 1,591 AIOM members, who were sent a questionnaire containing various clinical scenarios[28]. These scenarios were compatible with the preventive or therapeutic use of G-CSFs. A total of 350 interviewees (22%) completed the questionnaire, which highlighted the following data: about 70% said they would not have used (or would have rarely used) G-CSFs in the proposed clinical scenarios, and 58% would have used these drugs as secondary prophylaxis only after the appearance of neutropenia. Figure 1 shows the results of this survey. Furthermore, 36% of oncologists said they approved of reducing the doses laid down for elderly patients with febrile neutropenia, and 23.1% of changing their scheduled therapy.

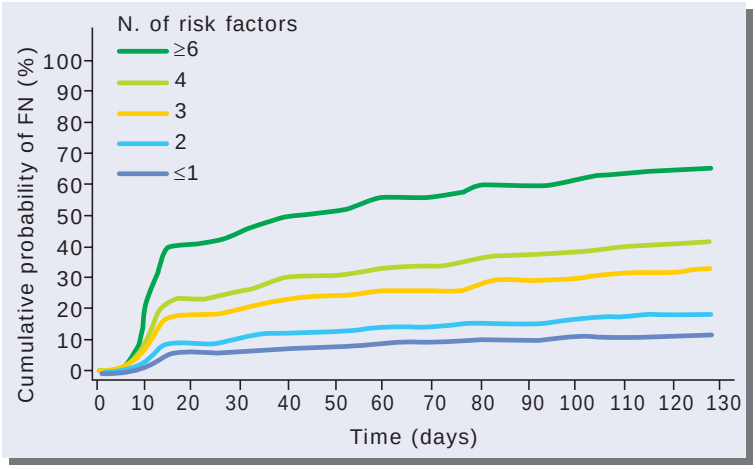
This result is a little worrying, since it is probably based on the assumption that the RDI (Relative Dose Intensity) can be decreased in elderly patients without running excessive risks, since tumour aggressiveness and growth is less extreme than in younger patients. In reality a great deal of experimental data and the clinical trials themselves suggest that this assumption is not correct, and that - neoplasia and stage being equal - the survival medians in elderly patients are similar to those observed in the younger patients. In a few cases (reduced *performance status*, concomitant diseases, etc), they are even seen to be lower[29,30]. Therefore exceptions to the therapeutic plan in the elderly may worsen the prognosis in a similar way to that observed in youngers.

Figure 1. Use of G-CSFs in oncological patients. (Data from M. Danova et al. 2005[28]).



On the whole, this survey shows that only a certain number of interviewees (30-50%) routinely use G-CSFs to treat neutropenia, generally for less than one week, whereas the guidelines suggest 14 days of prophylaxis or until the neutrophil count returns to normal, whichever the shortest. "*Proactive*" use of these factors in prophylaxis therefore seems to be moderate, with a trend towards even more cautious use in elderly patients, i.e. precisely those at greatest risk of febrile neutropenia (FN).

Figure 2. Cumulative probability of an episode of febrile neutropenia occurring on the basis of the number of risk factors. (Data from G.H. Lyman et al 2005[38]).



Febrile neutropenia predictive models

Today there is unanimous agreement concerning the advisability of using G-CSFs in the prophylaxis of chemo-induced neutropenia, as highlighted by the main consensus documents on the subject. The majority of trials and the various meta-analyses unanimously and consistently suggest that G-CSF administration reduces the incidence, duration and severity of cases of febrile neutropenia both in adult patients and pediatric neoplasias[31-33]. Conversely, the question of whether primary prophylaxis should be administered to all patients who start any treatment regimen or only to those undergoing particularly myelo-aggressive regimens or with numerous risk factors for FN is still open[34-36].

As things stand, there is no validated sufficiently reliable mathematical model able to predict the probability that a given patient may suffer an episode of neutropenia, but several trials are under way to put together a sufficiently sensitive model to identify patients at FN risk ³20%. The first attempt to validate a prediction model was made by Klastersky. The model was based on a system with eight parameters, each with its own score, and an overall maximum total of 26 points[37]. This model has proved to be very sensitive (80%), specific (71%) and has a positive predictive value (PPV) of 91% in low-intermediate risk patients. It is however less effective precisely in the patients at greatest risk.

More recently Lyman et al. analysed the febrile neutropenia risk factors of 577 patients with intermediate NHL, and identified six independent significant factors for FN[38,39]:

1. age > 65 years old;
2. kidney disease;
3. cardiovascular disease;
4. Hb levels < 12 g/l;
5. decrease in RDI ?80%;
6. no prophylaxis with G-CSF.

A series of curves was drawn up on the basis of the weight of each risk factor that describes the probability of an episode of febrile neutropenia occurring (figure 2).

At present, FN risk is assessed by consulting tables which contain the risk percenta-

Table 1. Classification of neutropenia with reference to neutrophil count.

Degree	Clinical severity	ANC (x 10^9/L)	
		NCI	OMS
0	None	>2.0	>1.5
1	Mild	≥1.5 <2.0	≥1.0 <1.5
2	Moderate	≥1.0 <1.5	≥0.75 <0.99
3	Serious	≥0.5 <1.0	≥0.5 <0.75
4	Risk of death	<0.5	<0.5

ge for each neoplasia/protocol. The recent update of the NCCN guidelines is useful for this[40].

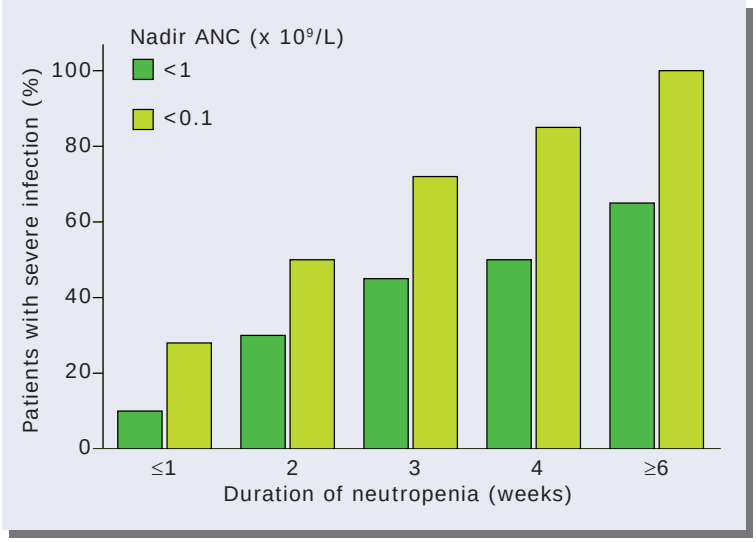
Consequences of neutropenia and G-CSF

Chemo-induced neutropenia (CIN) is one of the most frequent complications of cytostatic protocols and is the most frequent cause of decrease and delay in scheduled doses. Since the risk of infection is related to the duration and severity of the neutropenia, the National Cancer Institute (NCI) classification shown in table 1 is commonly accepted. It includes four degrees of severity according to absolute neutrophil count (ANC). The WHO classification is also used, which only partly overlaps with the previously mentioned system.
Although the risk of infection and therefore of febrile neutropenia increases progressively, it becomes very high from ANC values $<1.0x10^9$/l (NCI grade 3 or WHO grade 2). This aspect is both of clinical and methodological importance, since baseline risk has to be taken into account when interpreting neutropenia prevention efficacy trials. Figure 3 shows the comparison data obtained by Bodey in patients with acute leukaemia. This data allows the risk of infection to be related to neutrophil count and duration of neutropenia.

Febrile neutropenia

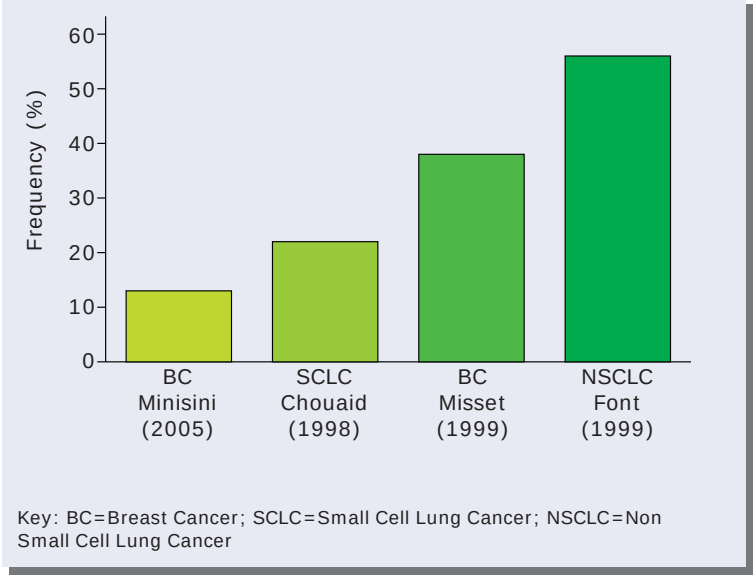
When the decrease in circulating neutrophils drops below a threshold value (0.5x109/l), conventionally adopted in large clinical trials, and the patient becomes feverish

Figure 3. Risk of infection with reference to absolute neutrophil count and duration of neutropenia: 10% of patients have a serious episode of infection right from grade 3 neutropenia (ANC <1.0x109/L), even if it only lasts a short time (<1 week) (Data from Bodey et al. 1966[41]).



(T > 38.2°C), the clinical condition is defined as febrile neutropenia (FN). Febrile neutropenia is a condition with high infection-related mortality. It calls for long periods in hospital, often in intensive care units, and considerably increases oncological patient management costs[42]. Furthermore, the outbreak of FN calls for a decrease in the doses of anti-

Figure 4. Rates of febrile neutropenia measured by various Authors in different populations and with different therapeutic regimens. (Data from Misset 1999[44], Minisini 2005[45], Font 1999[46] and Chouaid 1998[35]).



blastic drugs and/or for them to be deferred with respect to the scheduled protocol. This has a prognostic impact which can have considerable clinical importance and of which we have only become sufficiently aware in the last few years[12,43].

The incidence of febrile neutropenia is very high during the first treatment cycle, but it is a feared complication for the whole therapeutic schedule and should always be taken into consideration. FN risk depends on the neoplasia, antiblastic regimen and patient-related factors (age, concomitant diseases, etc). Figure 4 shows the incidence of febrile neutropenia in four different trials.

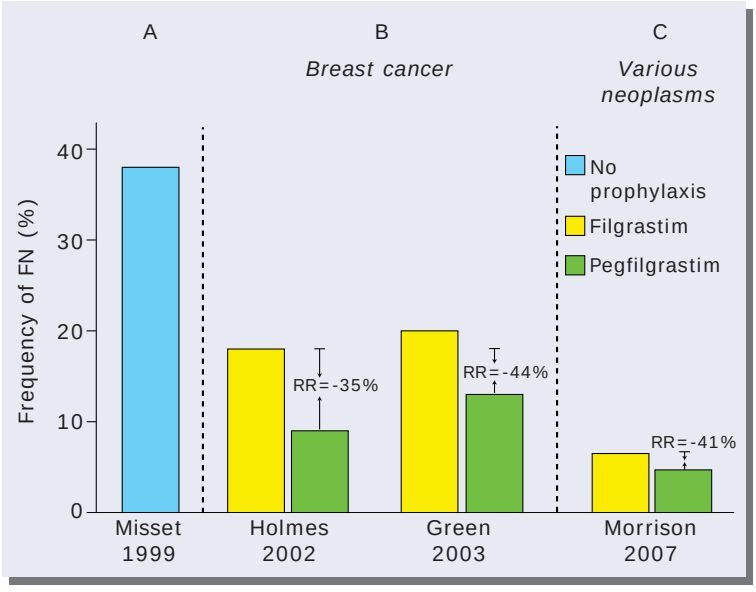
Impact of G-CSF on febrile neutropenia

All the myelopoietic growth factors tested up to now are able to decrease the incidence of chemo-induced neutropenia, both in adult patients and children, regardless of the underlying neoplasia and other risk factors[47-49]. Although both granulocyte colony-stimulating factors (G-CSF) and granulocyte macrophage colony stimulating factors (GM-CSF) are used, the majority of clinical trials have been performed with the former class of molecules.

Three molecules belong to the G-CSF class: filgrastim, its recent pegylated form (pegfilgrastim), and lenograstim. Pegfilgrastim is made by conjugating parental glycoprotein (20 kD) with a molecule of 19 kD polyethylenglycol (PEG). The complex macromolecule obtained weighs about 39 kD. Since the PEG molecule is essentially inert both from the point of view of chemical reactivity and with regard to three-dimensional structure, pegfilgrastim has the same ability to bind to the receptor on the granulocyte membrane, but is not filtered by the kidneys. Consequently it has a half-life of 46-62 hours, compared with filgrastim's half-life of 3-4 hours[50]. The pegylated form is eliminated by the neutrophils themselves. They hold the molecules bound to their surfaces and take them out of the bloodstream, therefore avoiding renal clearance. *To achieve the same level of stimulation and receptor voracity, pegfilgrastim may be administered to adults in a single dose (6 mg on day 2 of each chemotherapy cycle), while filgrastim is generally administered at a dose of 5 μg/kg/day for up to a maximum of 14 consecutive days.* Several studies have compared the effectiveness of the two regimens on neutrophil count normalization; figure 5 summarizes the results of comparative efficacy trials with these two molecules.

It is interesting to note that, if filgrastim is administered to breast carcinoma patients, it halves the incidence of febrile neutropenia compared to untreated patients (38% *vs.* 18%), and if pegfilgrastim is administered the incidence is reduced by about 70% (9-13%) when compared to the number of cases normally expected for this neoplasia in dose-finding

Figure 5. Risk of febrile neutropenia in patients with stage II-IV breast carcinoma treated with doxorubicin plus docetaxel. The risk of FN in this situation is about 38% if G-CSFs are not administered (light blue bar) (A). The two pairs of columns in the middle show the rates of FN after treatment with filgrastim (yellow bar) and pegfilgrastim (green bar) recorded in two different trials (B). The last pair of columns (C) refers to a large observational study (over 6,000 patients) with various neoplasias. The results of this trial have been reported because coming from the "real world" and all suggest a greater effectiveness of pegfilgrastim. (Data from Misset 1999[44], Green 2003[51], Holmes 2002[52] and Morrison 2007[33]).



trials (38%). These decreases in the incidence of febrile neutropenia correspond to a 40% better decrease in the relative risk (RR) for pegfilgrastim than for filgrastim, and 90% better decrease compared to no prophylaxis at all. In Morrison's very recent study, the rates of febrile neutropenia were examined in 6,148 patients affected with a broad spectrum of neoplasias and undergoing treatments with both molecules in various clinics/hospitals: again in this case, prevention with pegfilgrastim turned out to be a great deal more effective than treatment with filgrastim (4.7% *vs.* 6.5%; p=0.04), with a 41% decrease in RR[33]. If absolute risk is transformed into number of patients needed to treat (NNT) to avoid an episode of febrile neutropenia, it turns out that for every 56 patients treated with pegfilgrastim instead of filgrastim one episode of FN is saved. This value is extremely positive in terms of cost-benefit ratio: it should be considered that the use of aspirin in the prevention of acute myocardial infarction (a measure which is universally accepted to be very cost-effective) has similar NNT values to these[53] (table 2).

If pegfilgrastim is compared to no prophylaxis instead of filgrastim, the number of patients needed to treat is halved since, as we have seen, filgrastim itself halves the incidence of FN compared to no prophylaxis. Table 2 shows data comparing the decrease in absolute risk, and therefore in NNT, for molecules with an efficacy considered absolutely outstanding and irreplaceable. The favourable cost-benefit ratio of prophylaxis with pegfilgrastim is immediately clear if the costs of each treatment (shown in the table) for its respective duration and number of patients it is necessary to treat to prevent an episode are compared.

Mortality and rates of hospitalization

The death-rate related to an episode of febrile neutropenia is affected by several variables: severity of neutropenia, performance status and age of patient, as well as the rapidity and appropriateness of the therapeutic measures adopted. Several pharmacovigilance studies suggest that mortality among oncological patients with febrile neutropenia is still today in the neighbourhood of 7-11% [57,58]. In the majority of cases, death is directly related to infections. These are very often sepses caused by Gram-negative and positive germs and several yeasts and fungi (*Aspergillus* spp, systemic candidiasis, etc.).

Pegfilgrastim is found to be more effective than filgrastim in decreasing rates of hospitalization and antibiotic consumption.

In a recent retrospective analysis performed by Kuderer on the discharge records of a total of 41,779 adult patients in 115 oncological departments in the USA (1995-2000 period), 55,276 hospitalizations were recorded: 15% of these were attributed to episodes of febrile neutropenia[42]. The mean FN-related mortality was 11%, with relatively low rates for breast carcinoma (3.6%), considerably higher for lung carcinoma (13.4%) and even higher for leukaemias (14.3%). The average stay in hospital for these three conditions was 8 days, 8.3 days and 19.7 days respectively. It is therefore clear that the neoplasia and respective therapeutic regimen affect FN rates, days of hospital stay, mortality and case management costs. Table 3 summarizes the main data in this study.

Table 2. Comparison of cost effectiveness ratios measured as number of patients treated (NNT) to prevent one event. (Data from B. Dahlof 2002[54], W. Hacke 1999[55], and F Andreotti 2006[56]).

Drug	NNT	Event prevented
Pegfilgrastim *vs* filgrastim	56	1 episodio di FN
Aspirin + warfarin in ACS*	33	1 evento coronarico maggiore
Losartan *vs* atenolol in diabetics**	36	1 ictus
Thrombolysis within 4 hours from AMI	11	1 decesso

Key: * treatment for at least 3-24 mesi; **treatment for at least 4 anni; ACS=Acute Coronary Syndrome; AMI=Acute Myocardial Infarction

Table 3. Rates of mortality, lenght of hospitalization and costs associated with febrile neutropenia. (Data from Kuderer 2006[42]).

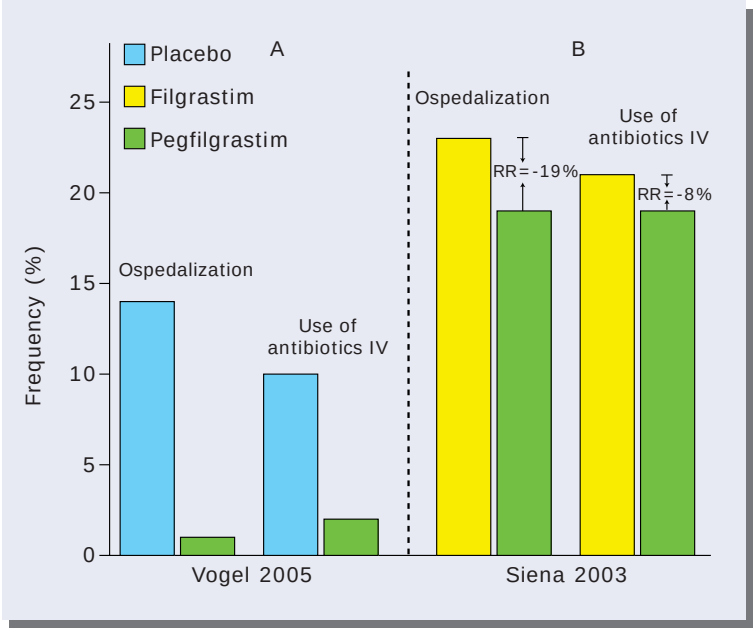
Neoplasia	Mortality (%)	Stay in hospital (days)	Costs ($)
Solid tumours (all)	8.0	8.1	13.354
Colorectal	8.8	9.3	12.850
Lung	13.4	8.3	10.976
Breast	3.6	8.0	12.372
Lymphomas (all)	8.9	10.7	18.437
Multiple myeloma	8.2	12.1	23.143
Leukaemias (all)	14.3	19.7	38.583

Affect of G-CSF on hospitalization and mortality

Rates of hospitalization. Prophylaxis with granulocyte colony-stimulating factors has been extensively shown to decrease both infection-related and overall mortality. Several studies have also shown a decrease in the rate of hospitalization and, when necessary, a shorter stay. This data comes both from individual clinical trials, and comparative assessments and meta-analyses[32, 59,60]. Regarding this, it is useful to compare the results of a large single clinical trial with data from a combined analysis of two more modest-sized trials[61,62]. The large clinical trial was conducted by Vogel et al. on a population of 928 breast carcinoma patients (docetaxel 100 mg/m2 every 3 weeks) randomly split between prophylaxis with pegfilgrastim or placebo[61]. Randomization with placebo was ethically possible since the expected FN risk with this protocol is between 10 and 20% ed inoltre lo studio è stato condotto prima delle recenti revisioni delle Linee Guida. The combined analysis was performed by Siena et al. on two trials (the previously mentioned trials by Holmes and by Green) which included an overall total of 448 patients[62]. The results obtained from these different assessments are shown in figure 6: panel A shows the results of the trial by Vogel et al, while panel B shows the results of the comparative assessment by Siena et al.

Infection-related mortality and overall mortality. The available data on mortality is still incomplete as things stand. and specially designed trials are needed. The data on infection-related mortality is encouraging, but not very significant since it is necessary to recruit large numbers of patients to achieve sufficient statistical power. However the scarcity of data should not mislead the clinician, since a decrease in the number of episodes of febrile neutropenia can only lead to a decrease in the number of infection-related deaths[63-65].

Figure 6. Effects of prophylaxis with pegfilgrastim vs. placebo (A) or pegfilgrastim *vs.* filgrastim (B) in breast cancer patients. Benefits are seen both as regards rates of hospitalization and use of intravenous antibiotics. (Data from Vogel 2005[61] and Siena 2003[62]).



A decrease in FN rates always turns into a decrease in days in hospital and in mortality.

In Sung's paediatric oncology meta-analysis performed with G-CSF and GM-CSF, no decrease in infection-related mortality was seen in patients with haematological neoplasias, while a moderate decrease in this parameter was seen in children with solid tumours[66]. The apparent neutrality of G-CSF prophylaxis on infection-related mortality is easily explained by the fact that patients at FN risk are carefully monitored and undergo extensive anti-infective therapies on an empirical basis as soon as the risk becomes clear, without waiting for lab test results. This attitude is confirmed by the higher parenteral administration of antibiotics and antifungals to patients who do not undergo G-CSF prophylaxis (table 4).

The data regarding the decrease in overall mortality rates is even more sketchy, since there are still no results from trials specially designed to measure this specific endpoint. Since overall mortality is affected by many parameters, we need trials with a sufficiently long follow-up and numerically suitable samples. Retrospective assessments and meta-analyses are of little use for this, since the trials used in these assessments do not form suitable material.

So far there has only been one trial on elderly patients with NHL split randomly between treatment with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and CHOP plus filgrastim, which showed an overall survival increase of 5 years in the second treatment group (24% *vs.* 22%; $p=0.76$)[67]. Larger studies are expected in the next few years.

Impact on quality of life

The relationship between neutropenia and worsening quality of life (QOL) has only recently been studied, when the results of several trials clearly showed that in moderate-serious neutropenias patients undergo a series of diagnostic and therapeutic procedures that are particularly physically invasive (bronchoscopies, bronchoalveolar lavage, biopsies, etc.) and psychologically demanding (sudden admission to hospital, fear of new infections, etc.)[68 and 69]. These aspects are even more significant in paediatric oncology. It is enough to consider the separation of children from their families and the impact of some of the procedures mentioned above.

The outbreak of febrile neutropenia also worsens some of the typical symptoms of neoplastic diseases and/or the relevant treatments, regardless of the control measures taken: asthenia, anorexia, vomiting, etc.[70,71]. So far there are no available results from trials with QOL as a fixed endpoint (apart from one), and there are no unique procedures specially validated for measuring this complex parameter. It is however evident that a decrease in episodes of FN and their shorter duration reflects positively on the quality of life of patients. The only trial we know of which has assessed the effect of G-CSFs on QOL was recently published by Martin et al. It includes 1,047 patients with breast carcinoma treated with FAC (5-fluorouracil, doxorubicin and cyclophosphamide) or TAC (docetaxel, doxorubicin and cyclophosphamide), with or without G-CSF prophylaxis72. QOL was assessed in this trial using two specific questionnaires validated by the EORTC: QLQ-C30 and QLQ BR-23. It was found that G-CSF prophylaxis significantly reduced the worsening of global health status (taken as a decrease of at least 10 points), and this decrease was particularly visible at the end of the scheduled treatment, especially with TAC (figure 7).

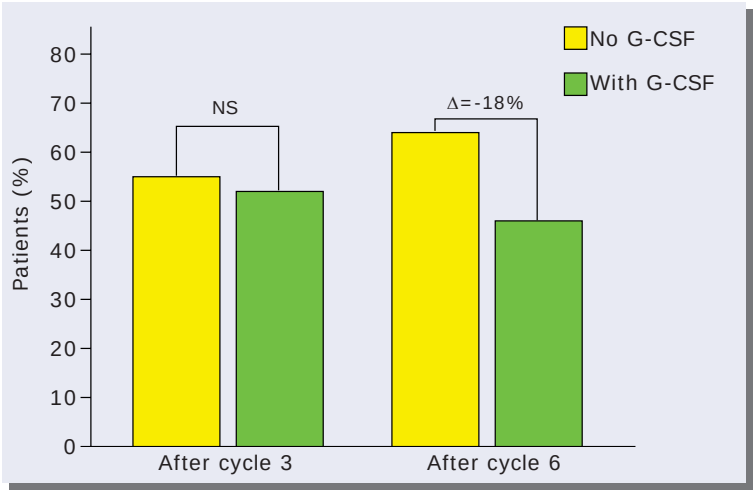
As figure 7 shows, the benefits of G-CSF prophylaxis on quality of life are seen right from the first cycles, but increase progressively as the antiblastic schedule continues. At the end of cycle 6, there is an 18% decrease (64% *vs.*

Table 4. Effects of G-CSF prophylaxis on various outcomes compared to placebo or no treatment. (Data from Sung 2004[66]).

Outcome	Effect (RR)	Significance (p)
Infections recorded	-22%	0.01
Use of amphotericin B	-50%	0.02
Infection-related mortality	+0.02	0.97

Pegfilgrastim prophylaxis is found to be highly effective and less expensive than both no strategy and filgrastim, even in the case of six-day filgrastim cycles.

Figure 7. Impact of G-CSF prophylaxis on the worsening of global health status (decrease of at least 10 points); only data relating to the impact of G-CSF on the TAC protocol after 3 and 6 cycles is shown. The vertical axis shows the percentage of patients with worsened GHS. (Data from M. Martin et al. 2006[72]).



46%) in patients who report a worsening in GHS ≥10 points.

Dose intensity and survival

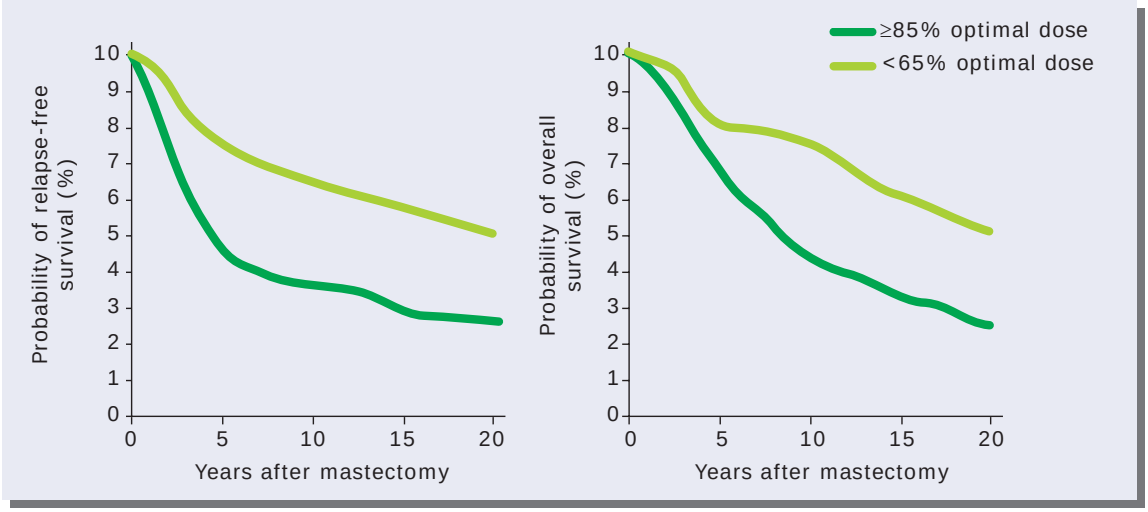
Relative dose intensity (RDI) has been seen to be an important indicator in determining the clinical course of a few neoplasias, particularly breast carcinoma, lymphomas and testicular sarcoma[73-75]. Neutropenia is one of the most frequent causes of failure to implement the RDI, and several trials have shown that G-CSF administration allows compliance with the scheduled doses and improvement in the prognosis (overall survival and event-free survival). The effects of decreasing the scheduled doses appeared in all their severity in the impressive twenty-year follow-up performed by Bonadonna et al. on patients with breast carcinoma treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), (figure 8).

This data was essentially confirmed in *the subsequent follow-up to 28.5 years recently published by the same researchers, which proves once again the absolute necessity of maintaining the RDI*[6].

Pegfilgrastim and dose intensity

The data from a recent prospective study on 2,112 adult patients with solid and haematological tumours subject to various protocols, all with pegfilgrastim as support treat-

Figure 8. Event free survival (EFS) and overall survival (GS) in breast cancer patients with reference to dose intensity: 20-year follow-up. (Data from G. Bonadonna et al. 1995[73]).



ment to prevent neutropenia, is useful for this[77]. The data in this study allowed the percentage of patients for which it was possible to comply with the RDI to be measured for a few neoplasias (breast carcinoma and NHL - table 5).
Brusamolino et al. reported even more interesting data for a group of 50 patients with diffuse B cell lymphoma treated with rituximab plus CHOP every 14 days (R-CHOP-14) along with pegfilgrastim support (6 mg/cycle) in all six scheduled cycles78. Overall survival after two years was particularly high in this trial (68%). This was also thanks to prophylaxis with pegfilgrastim, which allowed on-time administration of over 92% of cycles, with a practically optimal dose intensity. It was necessary to delay administration owing to neutropenia in only 3% of cycles.

Table 5. Dose intensity stratified by protocol in patients with NHL and breast carcinoma. (Data from Ozer 2007[77]).

Neoplasia/protocol	Mean RDI
NHL	
-(CHOP or R-CHOP)	77%
Breast carcinoma	
-AC (21 gg)	92%
-AC (14 gg)	94%
-Sequential AC and T (14 days)	87%

Key: RDI=relative dose intensity; AC=Doxorubicin+ cyclophosphamide; T=docetaxel; R=rituximab; CHOP= Cyclophosphamide, Doxorubicin, Vincristine and Prednisone.

Risk stratification and economic impact of G-CSFs

Since G-CSF administration reduces episodes of neutropenia and therefore the opportunistic infections related to it, it consequently leads to a decrease in hospitalization rates, in necessary antibiotic and antifungal treatments, and - to a not yet well defined extent - in mortality. It is therefore reasonable to expect that, besides the above described clinical benefits, early administration of G-CSF should have a favourable impact on patient management costs. If the number of days of hospitalization related to febrile neutropenia are known along with the costs/day in hospital, the costs of anti-infective therapies and mortality rates, it is possible to calculate the break-even threshold between cost of preventive G-CSF administration and cost of the events and complications prevented. The break-even point (or neutrality) therefore defines the exact moment when G-CSF administration becomes beneficial not just from the clinical viewpoint, but also economically. A preliminary analysis of the costs of filgrastim prophylaxis was published by Lyman in 1993[79]. This trial was able to show that filgrastim administration becomes cost neutral in 3 cases:

1. in patients with a ≥40% FN risk;
2. in patients previously admitted to hospital for febrile neutropenia (highly relapsing);
3. in all patients at increased FN risk (elderly and/or multiple risk factors).

Up until 2000 the guidelines of the American Society of Clinical Oncology (ASCO) gave the break-even point, i.e. the threshold beyond which G-CSF administration is cost effective, as 40% on the basis of these preliminary assessments[80]. In reality already back in 1998, a revision of the above mentioned data, which included laboratory costs, radiological diagnostic costs, nursing costs and the costs of other support measures actually recorded during hospitalization, reduced the cost-neutrality threshold considerably. In this later economic appraisal, filgrastim administration became cost effective for febrile neutropenia risk levels of nearly 23% (figure 9). Similar assessments performed by different authors and in different American hospitals gave essentially similar results. It is however evident that the costs of hospitalization are not the only ones that determine the break-even threshold, although they are the easiest to quantify. *For an accurate assessment of the bre-*

FN prophylaxis with myeloid growth factors is already cost effective at risk levels of 20% and it is likely that the introduction of pegfilgrastim will further lower the break-even threshold.

Figure 9. Analysis of filgrastim administration cost minimization in the prophylaxis of febrile neutropenia. The calculation refers to administration which begins during the first cycle of chemotherapy and the cost of hospitalization and associated treatments only, in 1993 (break-even threshold of 40%) and in 1996 (break-even threshold of 23%).

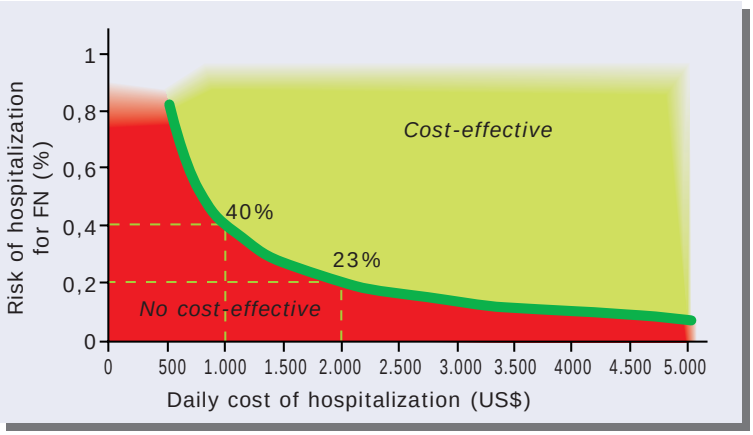
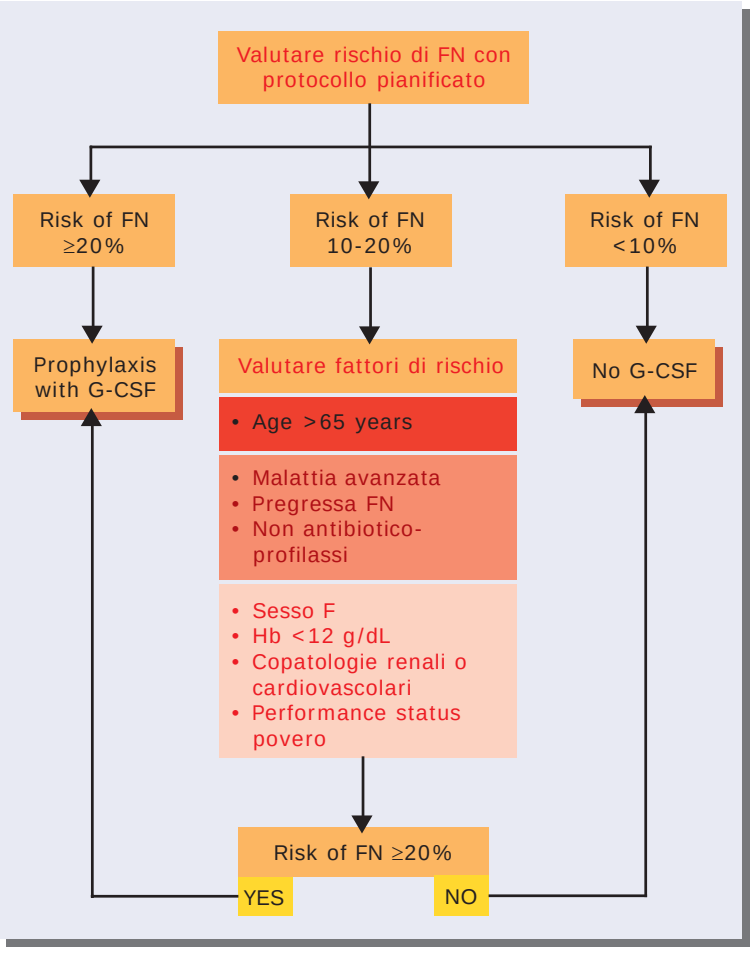


Figure 10. Febrile neutropenia risk assessment. The probability of an episode of FN must be calculated carefully in doubtful patients (10-20% risk): the guidelines are very clear on this, but an age > 65 years old is almost always a sufficient risk factor to start effective prophylaxis both from a clinical and economic point of view.



ak-even point between pharmaceutical costs and resources saved thanks to drug administration, indirect costs should also be considered (post-discharge family care or nursing costs, house calls and home treatment which the patient may have to pay for, loss of earnings owing to the working days lost, etc.).

Lastly it is worth noting that, while the cost of dispensing G-CSFs in hospital has remained essentially the same over the years, the cost/day of hospital care has increased in countries with advanced health systems at a rate of about 5-10% per year, thus constantly further decreasing the break-even threshold in favour of G-CSF prophylaxis. In the light of these considerations, both the ASCO and European (EORTC) guidelines have set values of ≥20% for the febrile neutropenia risk threshold after which G-CSF prophylaxis should be started (figure 10)[6,23].

Furthermore, for relatively young people with a long working life still ahead of them, the cost of FN-related death and the cost/year of life saved should be included in the equation. In a comparative study, Lyman et al. compared the costs/year of greater survival (cost for every year of life earned) thanks to G-CSF prophylaxis with those stemming from various other measures - all widely accredited - such as dialysis in patients with terminal kidney disease or tissue plasminogen activator (tPA) administration to patients with acute infarction. The results of this investigation (figure 11) showed that G-CSF prophylaxis administered to a 55 year old woman with breast carcinoma costs about US$ 34,000/year,

much less (-31%) than dialysis[39].

Economic impact of pegfilgrastim

Three types of granulocyte colony-stimulating factors indicated for the prophylaxis and treatment of febrile neutropenia are available in Italy today. Most of the information on these specific indications comes from trials with filgrastim. However, during the last three years, clinical trials with pegfilgrastim have increased. It is consequently today possible to make a few direct comparisons between these two molecules, both with regard to clinical response and economic aspects.
Although the guidelines suggest that G-CSF administration should last for 14 days or until the neutrophil count normalizes, in "actual practice" average filgrastim cycles last about 6-11 days[51, 52,61].
Besides the purchase price, an economic appraisal must take clinical efficacy into account, i.e. the greater number of episodes of febrile neutropenia avoided with the molecule that is more active than the reference molecule. Regarding this, it is interesting to consider the results of the GEPARTRIO trial[81], which was performed on a population of 1,256 women with breast carcinoma treated with the TAC protocol and randomly split into two different FN prophylaxis strategies:

1. 500 mg of ciprofloxacin twice a day for 10 days (days 5-14);
2. 5 µg filgrastim/kg/day for 6 days (days 5-10);
3. 6 mg pegfilgrastim in a single dose (day 2);
4. pegfilgrastim (as above) plus ciprofloxacin (as above).

The data from this study is particularly interesting because we have results for G-CSF prophylaxis according to "actual schedules" for the first time (figure 12). It is well known that, in daily practice, G-CSFs are administered for very much shorter periods than those suggested in the guidelines, both for reasons of cost and practicality. Figure 12 shows the results of the GEPARTRIO trial. The data from this trial is found on table 6 complete with relevant costs. It shows that if pegfilgrastim prophylaxis is used as a prevention strategy in a group of 100 women treated with TAC, there is a vast saving in economic resources (€ 74,072, compared to € 93,759 for the same group if 6-day filgrastim prophylaxis is used). If an episode of febrile neutropenia lasts about 10 days and 1 day in an oncological ward costs about €590, it is possible to simulate the costs of treating a group of 100 patients with filgrastim and pegfilgrastim (table 6).
Pegfilgrastim administration leads to a saving of about € 20,000 compared with filgrastim prophylaxis on a group of 100 patients (-20%). The

Figure 11. A year of life saved with G-CSF is more economical than a year of life saved with dialysis or with the CMF protocol administered to 75-year-old patients with breast cancer. (Data from G.H. Lyman 2000[39]).

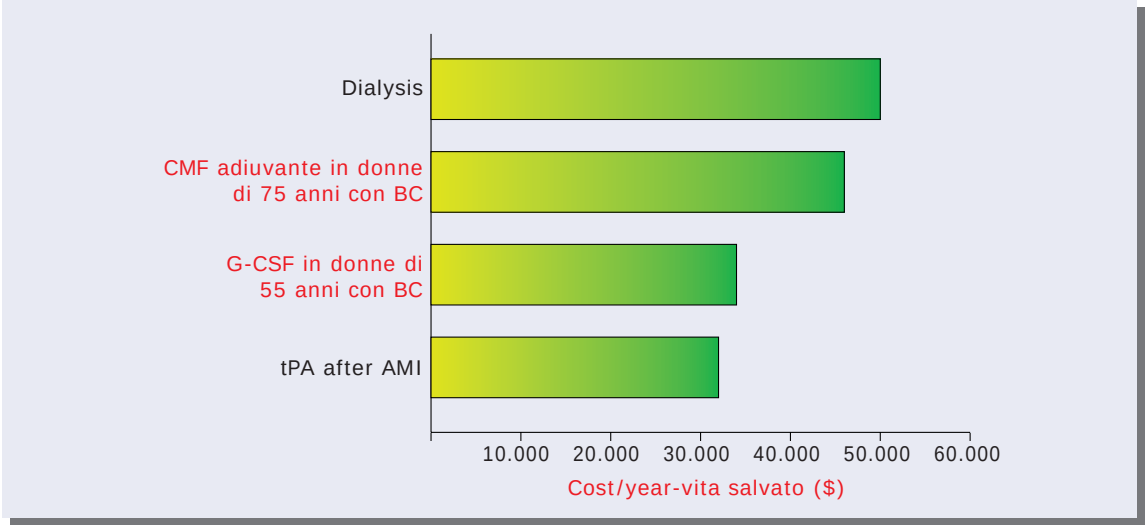
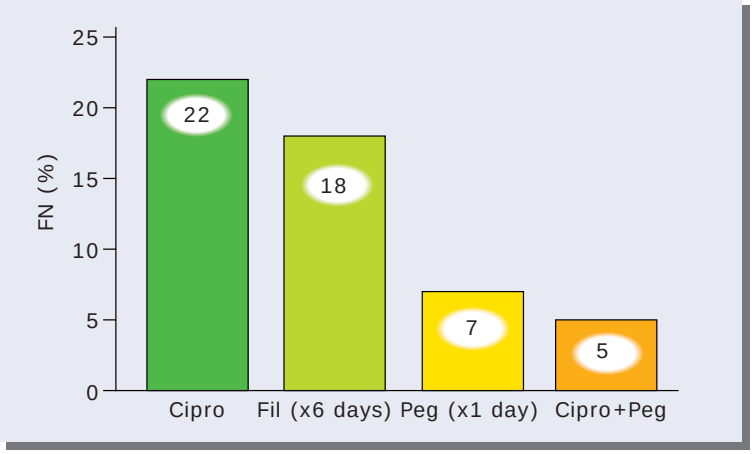


Figure 12. Episodes of febrile neutropenia observed with four different prophylaxis strategies. It is interesting to note that pegfilgrastim in a single dose reduced episodes of FN (7%) considerably more than filgrastim for 6 days (18%). La maggior parte degli episodi si è verificata nel 1° ciclo: 9% nel braccio filgrastim contro 2% nel braccio pegfilgrastim. (Data from Von Minckwitz et al. 2007[81]).



data in table 6 should be taken as rough, since several variables which would further increase the cost of managing the group treated with filgrastim have not been taken into account (higher costs for antibiotic and antifungal treatment, greater costs for identifying the infection site, etc.). The greater number of deaths which occurred due to the greater incidence of FN has also not been taken into account.
A similar scenario was hypothesized by other authors[82]. In a recent simulation by Chiroli et al. the cost-efficacy ratio of primary filgrastim prophylaxis, administered with two different durations (6 and 11 days), was assessed in a national prospective study (Italy) on patients with breast carcinoma and FN risk ≥20% in comparison with pegfilgrastim (single dose). Table 7 shows the results of this simulation with regard to the various end-points considered. Analysis of the data suggests that pegfilgrastim prophylaxis seems to be more economically beneficial than filgrastim, at least in Italy, even when the shorter strategy is considered (6 days).
Equally gratifying results have recently been reported in the prophylaxis of FN in patients with ovarian carcinoma[76]. This trial assessed the cost-efficacy ratio of pegfilgrastim in FN prophylaxis in patients with ovarian carcinoma treated with a protocol based on taxane plus carboplatin. Two different risk assumptions were made for febrile neutropenia: 5% risk and 16% risk. *The choice of a risk level < 20% in this simulation is particularly interesting since it assesses whether the 20% threshold set by the guidelines as the break-even point after which the prophylaxis becomes cost-effective may be lowered in this clinical setting.* This simulation hypothesizes a group of 10,000 women undergoing:

1. No prophylaxis;
2. primary prophylaxis (x 6 cycle);
3. secondary prophylaxis after an episode of FN.

Figure 13 shows the results of this simulation: it can clearly be seen that primary prophy-

Table 6. Primary prophylaxis with pegfilgrastim vs. filgrastim in a group of 100 patients.

Parameter	Prophylaxis	
	Filgrastim (1 ampoule x 6 days)	**Pegfilgrastim (1 ampoule = 6 mg)**
Patients treated	100	100
Expected FN episodes (1° cycle)	9	2
Total hospital days (~10 days/episode)	90	20
Cost of stay (€)[1]	53.100,00	11.800,00
Cost of prophylaxis (1° cycle) x 100 pts (€)[2]	40.659,00	62.272,00
Cost of managing the group	**93.759,00**	**74.072,00**

Key: 1=average cost of hospitalization for FN=€590,00 according to DRG; 2=hospital purchase price is 50% lower than the retail price; per pegfilgrastim prezzo max ospedaliero.

Table 7. Comparison of costs and outcomes after filgrastim administration (x 6 days and x 11 days) vs. pegfilgrastim in patients with breast carcinoma and ?20% FN risk. (Data from S Chiroli et al. 2006[82]).

Outcome	Strategy		
	Fil 6 days	Fil 11 days	Pegfil
Mean cost ($)	3.524	5.240	3.316
FN risk (%)	17,5	12,5	7
Life expectancy (years)	16,3	16,4	16,4
QALY	15,22	15,27	15,32

laxis is the most cost-effective strategy for 16% risk levels, and that secondary prophylaxis paradoxically turns out to be more expensive not only than primary prophylaxis, but also than "no prophylaxis". The overwhelming majority of the cost generated by an episode of neutropenia is attributable to the days in hospital, which this simulation did not hypothesize as occurring in an intensive care unit. Unfortunately this is not a rare occurrence and a lot more expensive per day than admission to a "medical ward".

This work is however also interesting for another aspect: if the results obtained with patients with a 5% FN risk are examined, it can be seen that the cost of primary prophylaxis with pegfilgrastim needed to prevent FN-related hospitalization is US$ 47,343. Even in patients at such low risk, this value is under the *US$ 50,000 threshold traditionally considered the divide between an acceptable and unacceptable measure from the economic point of view* (see previous figure 11).

G-CSF administration should be seen as an opportunity which goes beyond FN prevention, since it allows scheduled doses to be complied with, and this has a positive impact on the course of the disease.

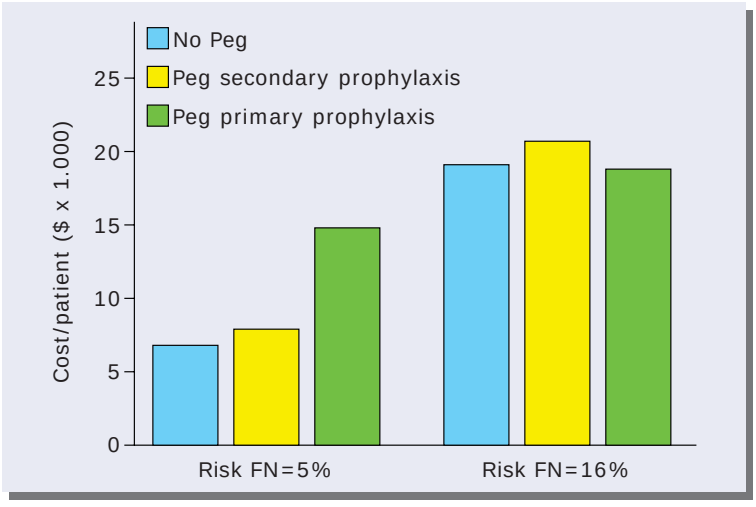
Conclusions

Over fifteen years after the introduction of myelopoietic growth factors in oncology, there is no doubt they have come to clinical attention as an essential clinical aid for achieving various therapeutic aims, including improving the quality and expectancy of remaining life. Today this class of drugs should also be considered an essential measure for decreasing the cost of managing oncological patients at medium risk of febrile neutropenia[12,13,43,84-86], considering the growing costs of hospitalization associated with each episode.

The introduction of a pegylated form of filgrastim seems to have kept all the promises, thanks to its simplicity of administration, greater patient compliance and essentially similar purchase cost to the non-pegylated form. Numerous trials seem to show that pegfilgrastim is more effective than its ancestor, perhaps owing to more constant stimulation of the granulocyte receptors.

When should prophylaxis begin? The guidelines agree on a 20% limit above which preventive administration of G-CSFs is effective from the clinical and economic points of view, but the results of numerous trials suggest this limit can be further lowered. TiM

Figure 13. Effects of three different prophylaxis strategies with pegfilgrastim after risk stratification. Secondary prophylaxis turns out to be cost effective in low-risk patients (<5%), whereas primary pegfilgrastim prophylaxis is more beneficial at a risk ≥16%. (Data from T.M. Numnum et al. 2007[83]).



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