Treatment of Febrile Neutropenia Is Expensive: Prevention Is the Answer

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Febrile neutropenia (FN) is among the most frequent complications during the administration of cytotoxic chemotherapy. In spite of major progress in the management of FN during the past three decades, FN remains associated with a significant frequency (up to 30–40%) of serious complications and a non-negligible mortality (overall 5–10%) [1]. Besides the morbidity and mortality associated with FN, the expenses resulting from its management are considerable and, most likely, the figures presented in many studies are underestimated [2].

A significant improvement to reduce human suffering and the economical burden of the management of FN has resulted from the possibility to predict accurately which patients are at a relatively low risk (> 5%) of developing serious complications during FN [3]. Such patients, who represent at least 60% of the whole patient population developing FN after chemotherapy, can be treated, in many cases, with orally administered antibiotics and without being hospitalized for prolonged periods of time [4]. This simplified approach has been shown to reduce the expenses resulting from the management of FN by about 45% [5]. Of course, for the patients with a predicted higher risk of severe complications during FN, hospitalization and empirical therapy with intravenously administered broad spectrum antibiotics remain the standard rules. These patients will also require more often intensive care support and some of them will eventually die from the complications of FN. This relatively small group of patients with complicated FN is actually responsible for the major proportion of the costs involved in the treatment of FN.

The most obvious solution for significantly decreasing the morbidity and mortality resulting from FN, is prevention. Effective prophylaxis of FN might also impact on the costs of management of FN, depending on how expensive it would be. The prophylactic administration of antibiotics, namely the fluoroquinolones, can significantly decrease the incidence of FN in patients with solid tumors [6] or lymphomas [7] and it is very cheap. However, the risks associated with the inevitable emergence of resistance make many experts reluctant to recommend this approach.

The use of granulocyte colony-stimulating factors (G-CSFs) is a physiologic approach for the prevention of FN. It has been shown in a recent meta-analysis to reduce the relative risks of FN by 46%, infection-related mortality by 45% and early deaths by 40% [8]. In the pivotal placebo-controlled study by Crawford et al. [9], the incidence of confirmed infections was reduced by approximately 50% when a G-CSF was given.

Because G-CSFs are expensive, the criteria for their use have been based on purely economic grounds (i.e. cost savings), using, as the reference, the cost of the initial hospitalization for FN [2]. Although initially the threshold for recommending the prophylactic use of G-CSFs was a 40% risk of developing FN, presently most official guidelines, namely those proposed by the EORTC (European Organization for Research and Treatment of Cancer), recommend as the standard threshold a 20% risk [10]. According to these standards, patients with lower risks of developing FN after chemotherapy are not eligible for prophylaxis with G-CSFs, unless they are older than 65 years and/or present serious co-morbid conditions.

However, once FN occurs the frequency of severe complications and the risk of death are not reduced in those patients having a risk of FN lower than 20% [11]. Thus the present recommendations leave a very large population of patients – actually the majority of solid tumor patients receiving standard chemotherapy – with no protection against the consequences of FN, raising the question whether the indications for the use of G-CSFs for prevention of FN should not be extended [12].

The paper by Ihbe-Heffinger in this issue of ONKOLOGIE [13], raises several interesting questions regarding the cost of FN and actually provides some responses about how to deal with it. The authors evaluated 325 consecutive patients and focused on 58 episodes of FN to evaluate the costs. While the incidence reported for FN in their patients with lymphoma (22%) or aggressively treated breast cancer (27%) matches what is usually reported in the literature [14, 15], it is surprising that most of those patients with breast cancer and lymphoma

did not receive a prophylaxis with G-CSFs, as the risk of FN was greater than 20%. It is also interesting to notice that 55 out of 58 episodes of FN were associated with at least one hospital stay, since hospitalization is no longer the standard for many patients with solid tumors experiencing FN during the course of standard chemotherapy [4, 5]. Finally, as the cost of medical care varies from country to country, the data provided by Ihbe-Heffinger et al. [13] are very useful to show the average situation in Germany for 3 common malignancies. Overall, the results match what is published elsewhere [2], with the caveat that these costs may be underestimated if the whole downstream neutropenia care is not fully taken into account.

The data allow, in addition, a speculative exercise about the cost effectiveness of G-CSF prophylaxis, would it have been given to all the patients in this series.

Actually, the mean cost of hospitalization, based on the author's data, was 138,250 € for lymphomas, 32,643 € for lung cancer and 25,578 € for breast cancer patients, totalizing 196,471 € (table 1). If we consider that G-CSF prophylaxis would have been effective in preventing 50% of the episodes of FN, the cost of management would then be 98,235 €. To these expenses should be added the cost of the G-CSF; if the sum would be inferior to the total cost of management reported here (196,471 €), the strategy could be considered as cost-effective. The standard cost of G-CSF (e.g. filgrastim) is 900 € for 5 administrations of 300 µg (price in Germany, 2011). This means a total cost of prophylaxis for 325 patients, in this series, of 292,500 €; this makes thus such a prophylaxis non cost effective, by strictly economic considerations that do not take into account the potential reduction in morbidity and mortality resulting from the use of G-CSFs.

Table 1. Actual and estimated costs of management of febrile neutropenia (FN) for a cohort of 325 patients receiving chemotherapy

Actual cost ^a	196,471
Estimated cost if primary prophylaxis (PP) with G-CSF is given to 325 patients ^b	98,235
Estimated cost if PP is given to 325 patients but 50% of patients with FN are treated ambulatory ^c	73,674

^aAs reported in [13].

^bIt is considered that PP reduces the frequency of FN by 50%.

^cIt is estimated that ambulatory care reduces the cost of management by 50%.

Table 2. Cost of primary prophylaxis for 325 patients with an original G-CSF or a biosimilar G-CSF at standard (5 × 300 µg) or reduced (2 × 300 µg) dosage

G-CSF		Dosage		Cost ^a , €	Minimum reduction of FN required for G-CSF primary prophylaxis be effective, %
Original	biosimilar	standard	reduced		
X		X		292,500	
X			X	117,000	60
	X	X		172,250	88
	X		X	68,900	35

^aIn Germany, 5 × 300 µg of G-CSF (e.g. Neupogen, Amgen GmbH, Munich, Germany) costs 900 €, and 5 × 300 µg of a biosimilar (e.g. Ratiograstim) costs 530 €.

What can be done to extend the potential benefit of G-CSFs to patients with a relatively low risk of FN? Some studies, although retrospective, have suggested that, in patients with a relatively low risk of FN, a limited dosage of G-CSF (such as 2 administrations, on days 8 and 12 after chemotherapy) might be effective [16]. If we apply that concept to our series, as shown in table 2, the cost of the primary prophylaxis would now be 117,000 €, which is still not cost effective, even if 50% of the patients with FN would be treated with ambulatory care (table 1). Further, more affordable G-CSFs (the so-called biosimilars) are now available, reducing the cost of G-CSFs substantially (e.g. 300 µg Ratiograstim, Ratiopharm, Ulm, Germany, costs 106 €); this would further help with cost-effectiveness.

Thus, as summarized in table 2, a reduced dosing (2 injections) with a standard G-CSF, would cost 172,000 € (not cost-effective) but, with a less expensive biosimilar, it would cost 68,900 €, which is cost-effective. With the possibility of treating a significant proportion of the patients in the ambulatory setting, this prophylactic approach, combining a biosimilar G-CSF and a reduced dosage might prove even more cost saving.

As shown in table 2, we also calculated the minimum reduction of FN that would be required for G-CSF primary prophylaxis to be cost-effective with the different schedules proposed. Actually, the reduced dosage schedule would require a reduction of 60% of the incidence of FN with the standard G-CSF and only 35% with the biosimilar. Of course 'Papaldo's hypothesis' [16] needs to be confirmed in prospective clinical studies, although in common practice, a reduced dosing of G-CSF is already used empirically by many oncologists today [17].

In conclusion, the cost-analysis of FN by Ihbe-Heffinger provides an outstanding opportunity to challenge our present concepts for the prevention and management of FN in the future. Joined efforts between the clinical and industrial worlds should be encouraged to provide optimal protection against FN-associated morbid consequences in the vast majority of patients receiving chemotherapy for common neoplastic diseases.

Disclosure Statement

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