

PEGFILGRASTIM – A HEALTH ECONOMIC MODEL TO ASSESS OVERALL COST-EFFECTIVENESS

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Febrile neutropenia (FN) is a serious adverse event of chemotherapy. A model applied in France and the UK demonstrated FN prophylaxis with one dose pegfilgrastim was less expensive yet more effective for reducing FN than 11 days of filgrastim in patients with early breast cancer at $\geq 20\%$ risk of FN.

FEBRILE NEUTROPENIA – COSTS TO PATIENTS AND THE HEALTHCARE SYSTEM

Myelosuppression leading to severe neutropenia (low neutrophil count) or febrile neutropenia (FN) (low neutrophil count and fever, indicators of potential infection) is the most serious toxicity of chemotherapy. Recent reports suggest that the risk of developing FN varies, depending on various factors including tumour type, the chemotherapy regimen used, cycle and dose of chemotherapy, as well as patient-related factors including elderly age, history of previous FN episodes and comorbidities [1, 2]. As FN is associated with substantial morbidity and mortality [3] it represents a medical emergency. Standard clinical practice for treating FN consists of administration of antibiotics, either in hospital or as ambulatory treatment depending on the patient's risk of complications, as defined by their Multinational Association for Supportive Care in Cancer score. Its management is therefore associated with a significant cost to the healthcare system and it also adversely affects the patient's health-related quality of life [4]. Neutropenia may also necessitate chemotherapy dose delays and/or reductions in subsequent treatment cycles, which is of importance as the delivery of suboptimal chemotherapy, i.e. low relative dose intensity [RDI], can result in poorer patient outcomes in terms of both disease-free and overall survival [5]. The prevention of

chemotherapy-induced FN should be considered a clinical priority, as it will help reduce hospitalisations and improve quality of care.

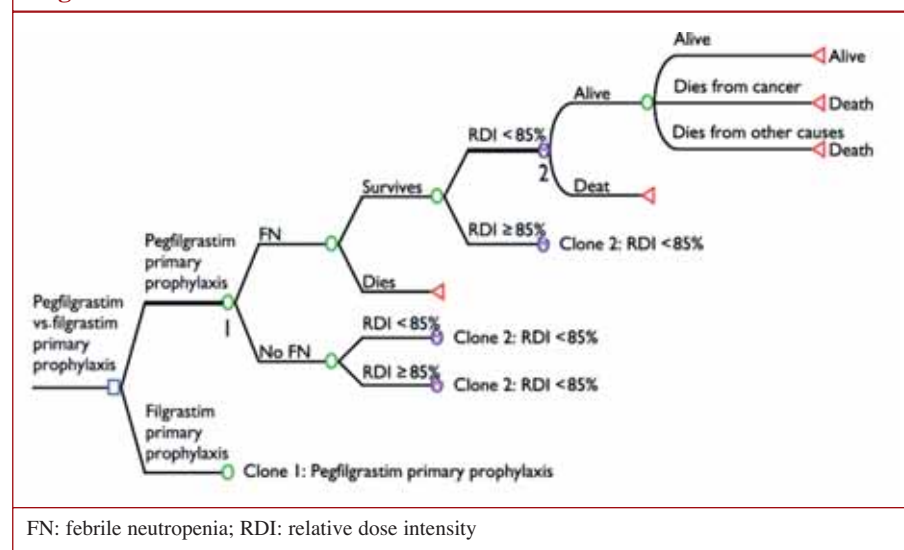
MINIMISING RISK OF FN

Granulocyte-colony stimulating factors (G-CSFs) stimulate an increase in circulating neutrophils. A recent meta-analysis showed that primary G-CSF prophylaxis decreases the severity and duration of chemotherapy-induced neutropenia as well as the incidence of FN in patients with solid tumours and lymphomas [6]. Recent guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network and European Organisation for Research and Treatment of Cancer (EORTC) recommend prophylaxis with G-CSFs from the first cycle when overall risk of FN from patient-related factors and chemotherapy is $\geq 20\%$ [7-9]. Prophylaxis can be given via a standard daily G-CSF injection, e.g. filgrastim (Neupogen) or lenograstim (Granocyte). Daily G-CSF treatment should be initiated 24 hours following chemotherapy and given daily until the patient's absolute neutrophil count has recovered within the normal range [10]. An alternative is the administration of a pegylated agent which is given once per chemotherapy cycle, i.e. pegfilgrastim (Neulasta). Results from two non-inferiority trials in patients with breast cancer showed similar efficacy for

pegfilgrastim compared with daily G-CSFs in terms of reducing the incidence and duration of FN in patients undergoing chemotherapy [11, 12]; in contrast, others have reported efficacy benefits for pegfilgrastim [6, 13, 14]. In addition, pegfilgrastim may offer improved convenience and help to ensure optimal dosing.

The acquisition cost of G-CSFs can appear expensive at face value. A previous cost minimisation study concluded that pegfilgrastim was cost-saving when risk of FN was high or when filgrastim treatment was administered for 11 days [15]. However, this study ignored some of the benefits of pegfilgrastim and did not take into account the fact that relatively short courses of fil-

Figure 1: Model structure



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Table 1: Effectiveness input data [18, 20]

Risk of febrile neutropenia (FN)	
Without G-CSF	24%
With pegfilgrastim	7%
With 11 days of filgrastim	12.5%
With 6 days of filgrastim	17.5%
FN case-fatality among hospitalised FN patients	
RDI <85%	
Among patients who experience neutropenia	40%
Among patients who have no neutropenia	9%
Among patients receiving pegfilgrastim	11.1%
Among patients receiving 11 days of filgrastim	12.7%
Among patients receiving 6 days of filgrastim	14.2%
Impact of RDI <85% on long-term survival	
Utility scores	
Breast cancer during chemotherapy	0.70
FN hospitalisation	0.33
Breast cancer in years 1–5	0.86
Breast cancer after year 5	0.96

FN: febrile neutropenia; HR: hazard ratio; RDI: relative dose intensity; RR: relative risk

Table 2: Cost-effectiveness of pegfilgrastim versus filgrastim in France^a [20]

	Pegfilgrastim vs. filgrastim 11 days	Pegfilgrastim vs. filgrastim 6 days
Incremental total cost/saving (% difference)	-Euros 1,450 (-21%)	+Euros 1,081 (+26%)
ICER per 1% reduction in absolute FN risk	Pegfilgrastim is dominant ^b	Euros 103
ICER per FN event avoided	Pegfilgrastim is dominant ^b	Euros 10,295
ICER per QALY	Pegfilgrastim is dominant ^b	Euros 10,810
ICER per LYG	Pegfilgrastim is dominant ^b	Euros 10,295

FN: febrile neutropenia; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; LYG: life year gained
^aFor France, the unit costs were collected using the following national public databases: Diagnosis-Related Group national cost database and French PMSI medical programme information system, year of valorisation for filgrastim: 2006, year of valorisation for pegfilgrastim: 2004.
^bPegfilgrastim is less expensive than 11 days of filgrastim.

grastim are often given in clinical practice, which are perceived to be associated with lower costs [14, 16]. It is important to note though, that such short durations of treatment are probably suboptimal as data from clinical trials suggest that patients require a median of 11 days of filgrastim treatment to achieve neutrophil recovery [13].

DEVELOPMENT OF A MODEL OF G-CSF USE IN BREAST CANCER

Here, we review a decision-analytic, cost-effectiveness model that was developed from the French and UK healthcare payer's perspective to assess the relative clinical outcomes and costs of primary prophylaxis with pegfilgrastim compared with two different strategies of daily G-CSF (filgrastim) treatment. The base case was for a 45-year-old woman with Stage II breast cancer receiving four cycles of chemotherapy with a $\geq 20\%$ risk of FN. The model simulated clinical outcomes and life expectancy in a cohort of women with breast cancer and follows them until death (either from cancer or other causes). It was assumed that during each chemotherapy cycle, patients may develop FN with a risk of dying from that event (see Figure 1). The model also included the probability of receiving optimal or sub-optimal chemotherapy doses based upon the RDI (the amount of chemotherapy delivered relative to the standard amount of chemotherapy over a specific time interval). Data suggest a link between receiving the planned chemotherapy dose intensity and disease-free and overall survival in patients with breast cancer [17].

MODEL DATA INPUT AND ASSUMPTIONS

Effectiveness data inputted into the model were based on the literature and/or validated by an expert panel (see Table 1). Pegfilgrastim was more effective than filgrastim, being associated with a 5.5% decreased risk of FN compared with 11 days of filgrastim [13] and a 10.5% decreased risk of FN compared with six days of filgrastim and therefore also decreased risk of FN-related mortality [14]. It was also assumed that pegfilgrastim was associated with a reduced likelihood of a patient receiving a chemotherapy RDI <85% (-1.6% and -3.1% reduced risk versus 11 or 6 days of filgrastim, respectively) and therefore improved long-term survival [17–20]. Breast cancer mortality and all-cause mortality were obtained from official national statistics. Costs were computed from both a French (2004–2006) and a UK (2006) healthcare payer's perspective and were restricted to reimbursed direct costs including drugs, drug administration, FN-related hospitalisations and subsequent medical costs.

Incremental cost-effectiveness ratios (ICERs; the difference in cost divided by the difference in effectiveness), were calculated for both countries and a discount rate of 3% applied (to adjust for costs occurring at different points in time). The robustness of the model

Table 3: Cost-effectiveness of pegfilgrastim versus filgrastim in the UK^a [18]

	Pegfilgrastim vs. filgrastim 11 days	Pegfilgrastim vs. filgrastim 6 days
Incremental total cost/saving (% difference)	-GBP 1,119 (Euros 1,231) (-26%)	+GBP 441 (Euros 485) (+16%)
ICER per 1% reduction in absolute FN risk	Pegfilgrastim is dominant ^b	GBP 42 (Euros 46)
ICER per FN event avoided	Pegfilgrastim is dominant ^b	GBP 4,200
ICER per QALY	Pegfilgrastim is dominant ^b	GBP 4,161 (Euros 4,576)
ICER per LYG	Pegfilgrastim is dominant ^b	GBP 3,955 (Euros 4,350)

FN: febrile neutropenia; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; LYG: life year gained.

^aDrug costs were obtained from the British National Formulary tariff; cost of drug administration, cost of FN hospitalisation, and subsequent cost after an initial FN hospitalisation were all obtained from the literature; year of valorisation for filgrastim and pegfilgrastim: 2006.

^bPegfilgrastim is less expensive than 11 days of filgrastim.

was assessed using one-way and multi-way sensitivity analyses to assess whether findings were replicated when model inputs were varied over a likely range.

COST-EFFECTIVENESS OF PEGFILGRASTIM VERSUS FILGRASTIM IN FRANCE AND THE UK

France

When tested in France, under base-case assumptions, this model showed that the overall cost of treatment was Euros 1,450 less for pegfilgrastim versus an 11-day course of filgrastim (Euros 5,302 vs. Euros 6,752) and was Euros 1,081 more expensive when compared with a six-day course (Euros 5,302 vs. Euros 4,221). Pegfilgrastim was dominant (less expensive as well as more effective) over 11 days of filgrastim in terms of cost per FN event avoided, per life-year gained (LYG) and per quality-adjusted life year (QALY) gained (see Table 2). Compared with six days of filgrastim, pegfilgrastim was cost-effective for all outcomes and can be considered a cost-effective strategy in France with respect to the threshold commonly accepted by European healthcare authorities (Euros 40,000/QALY gained). These results were robust to various sensitivity analyses, with pegfilgrastim becoming more cost-effective the higher the patient's risk of FN. In the comparison with 11 days of filgrastim, the model was also sensitive to the cost of filgrastim; when compared to six days of filgrastim results were most sensitive to the cost of pegfilgrastim and filgrastim, FN case fatality and base-line FN risk.

UK

When tested in the UK, under base-case assumptions, this model showed that the overall cost of treatment was GBP 1,119 (Euros 1,231) less for pegfilgrastim versus an 11-day course of filgrastim (GBP 3,196 vs. GBP 4,315; Euros 3,515 vs. Euros 4,746) and was GBP 441 (Euros 486) more expensive when compared with a six-

day course (GBP 3,196 vs. GBP 2,754; Euros 3,515 vs. Euros 3,029) [18]. Once again, pegfilgrastim was less expensive and more effective compared with 11 days of filgrastim in terms of cost per FN event avoided, per LYG and per QALY gained and was cost-effective compared with six days of filgrastim (see Table 3). Pegfilgrastim can therefore be considered a cost-effective strategy in the UK with the cost of GBP 4,161 (Euros 4,576) /QALY versus six days of filgrastim being very favourable compared with the cost-effectiveness threshold commonly used by UK healthcare authorities (GBP 30,000/ Euros 32,995/QALY gained). These results were also robust to changes in model inputs.

IMPLICATIONS OF THE MODEL FOR CLINICAL PRACTICE

Biological agents such as G-CSFs are often perceived as costly – particularly second-generation agents such as pegfilgrastim. However, when assessing overall cost-effectiveness, it is necessary to take into account the potential benefits that may be gained as a result of a reduction in the frequency and duration of FN episodes. This could result in savings in terms of reduced drug costs and a reduction in the overall cost of managing FN. Furthermore, there will often be a 'willingness-to-pay' for potential improvements in survival and so this is also an important consideration. This model was applied in two large European countries and showed that at 2006 prices, pegfilgrastim given once per chemotherapy cycle was cost-saving in comparison with 11 days of filgrastim and cost-effective compared with six and 11 days of filgrastim. These results were also found to be robust to various sensitivity analyses. There are, however, important differences in clinical practice between France and the UK. For example, the UK public health system is generally more cost-conscious, and it is therefore particularly important to demonstrate potential cost savings associated with any treatment in the UK, or to show that any additional costs taken onboard are accompanied by tangible clinical benefits. The UK Department of Health has, in fact, recently increased reimbursement for the treatment of FN to GBP 4,682 (Euros 5,189)/episode, which suggests that the current cost assumptions in the UK model underestimate the true cost of FN. A re-analysis of the model using the current UK Department of Health prices may allow demonstration of improved cost-effectiveness. Demonstration of cost-effectiveness is not critical in France from the reimbursement perspective, but the fact that an intervention is either dominant or cost-effective within the standard European definition (as we have shown here), is reassuring to institutions and payers. Interestingly, a

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new commission for health economics has recently been set up in France, which may also lead to a greater focus on health technology assessments here. Importantly, the model shows that the increased efficacy and convenience of pegfilgrastim versus six days of filgrastim in terms of FN risk and FN-related mortality comes at an acceptable price. Recent ASCO [7] and EORTC [8] clinical practice guidelines recommend prophylaxis with G-CSFs when a patient's overall risk of FN is $\geq 20\%$ or higher, but fall short of recommending any specific agent within this class. It appears important that future guidelines consider the long-term implications of any potential differences within the G-CSF class of agents when making future recommendations.

CONCLUSION

Our decision-analytic model showed that in France or the UK, primary prophylaxis with pegfilgrastim is less expensive and more effective than prophylaxis with 11 days of filgrastim and is also cost-effective compared with six and 11 days of filgrastim treatment, when taking into account the reported clinical benefits of pegfilgrastim. In these countries, pegfilgrastim should therefore be considered a cost-effective strategy for primary prophylaxis of FN in women with early breast cancer who are undergoing chemotherapy associated with an overall risk of FN $\geq 20\%$. Health economic models are useful in determining the full picture about the costs associated with any drug and demonstrate that while pegfilgrastim may appear expensive at face value, these costs may be offset by savings in other areas.

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