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Whyte, S, Cooper, KL, Stevenson, MD et al. (1 more author) (2011) Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in patients with non-Hodgkin's lymphoma in the United Kingdom (UK). Discussion Paper. HEDS Discussion Paper (11-02). (Unpublished)

HEDS Discussion Paper 11-02

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Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in patients with non-Hodgkin's lymphoma in the United Kingdom (UK)

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Abstract

Introduction: We report a cost-effectiveness evaluation of granulocyte colony-stimulating factors (G-CSFs) for prevention of febrile neutropenia (FN) following chemotherapy for non-Hodgkin's lymphoma (NHL) in the United Kingdom (UK).

Methods: A mathematical model was constructed simulating the experience of patients with NHL undergoing chemotherapy. Three strategies were modelled: primary prophylaxis (G-CSFs administered in all cycles); secondary prophylaxis (G-CSFs administered in all cycles following an FN event), and no G-CSF prophylaxis. Three G-CSFs were considered: filgrastim; lenograstim and pegfilgrastim. Costs were taken from UK databases and utility values from published sources with the base case analysis using list prices for G-CSFs and a willingness to pay (WTP) threshold of £20,000 per QALY gained. A systematic review provided data on G-CSF efficacy. Probabilistic sensitivity analyses examined the effects of uncertainty in model parameters.

Results: In the base-case analysis the most cost-effective strategy was primary prophylaxis with pegfilgrastim for a patient with baseline FN risk greater than 22%, secondary prophylaxis with pegfilgrastim for baseline FN risk 8-22%, and no G-CSFs for baseline FN risk less than 8%. Using a WTP threshold of £30,000, primary prophylaxis with pegfilgrastim was cost-effective for baseline FN risks greater than 16%. In all analyses, pegfilgrastim dominated filgrastim and lenograstim. Sensitivity analyses demonstrated that higher WTP threshold, younger age, or reduced G-CSF prices result in G-CSF prophylaxis being cost-effective at lower baseline FN risk levels.

Conclusions: Pegfilgrastim was the most cost-effective G-CSF. The most cost-effective strategy (primary or secondary prophylaxis) was dependent on underlying FN risk level, patient age, and G-CSF price.

Key words: Cost-effectiveness; economic model; febrile neutropenia; granulocyte colony–stimulating factors; prophylaxis; non-Hodgkin's lymphoma.

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INTRODUCTION

Neutropenia is the major dose-limiting toxicity of many chemotherapy regimens. Febrile neutropenia (FN) and its consequences are associated with substantial morbidity, mortality, and costs.(1) Chemotherapy-induced neutropenia and FN are also associated with dose reductions and delays to chemotherapy that may compromise patient survival.(2) In the UK the National Confidential Enquiry into Patient Outcome and Death performed a review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy (SACT). (3) They report that the most commonly reported grade 3-4 toxicities associated with patients dying within 30 days of chemotherapy were neutropenia, neutropenic sepsis and infection.

Recombinant human granulocyte colony-stimulating factors (G-CSFs) stimulate production of mature, functional neutrophils (4) which reduce the duration and severity of neutropenia and the incidence of FN when used as prophylaxis alongside chemotherapy.(5;6) G-CSF prophylaxis may be beneficial during treatment for many different cancers, depending on the risk of FN which is related to both chemotherapy regimen and patient risk factors.(7) This analysis focuses on non-Hodgkin's lymphoma (NHL) as the evidence base for G-CSF prophylaxis is well developed in this setting. Three G-CSFs were in use at the time of this analysis: filgrastim, pegfilgrastim, and lenograstim. Pegfilgrastim is given as a single injection per chemotherapy cycle. Filgrastim and lenograstim prophylaxis both involve administration of a number of daily injections per cycle. It is recommended that filgrastim and lenograstim are given daily until the neutrophil count returns to the normal range (for up to 14 days per cycle for filgrastim, or up to 28 days for lenograstim). (8;9)

G-CSFs can be administered as primary prophylaxis (in all cycles) or as secondary prophylaxis (in all remaining cycles following an episode of FN). In the UK, patients receiving chemotherapy for NHL often receive secondary G-CSF prophylaxis.(10) Clinical guidelines on the use of G-CSFs have been produced by the European Organisation for Research and Treatment of Cancer (EORTC)(7) and also in the US by the American Society of Clinical Oncology (ASCO)(11) and the National Comprehensive Cancer Network (NCCN) (12). All sets of guidelines recommend that prophylactic G-CSFs should be used where the risk of FN associated with the chemotherapy regimen is greater than or equal to 20%, and may be considered where the risk is 10-20%, particularly where additional patient risk factors are present.

The objective of this study is to model the cost-effectiveness of G-CSF prophylaxis of FN in patients with NHL compared with no use of G-CSF prophylaxis during treatment. This follows on from a study of the cost-effectiveness of G-CSF prophylaxis of FN in patients with breast cancer.(13) In the analyses seven prophylaxis strategies are evaluated: primary prophylaxis and secondary prophylaxis for each of three G-CSFs (pegfilgrastim, filgrastim and lenograstim) and no G-CSF prophylaxis.

This study focuses on high-grade (aggressive) NHL for which most patients undergo chemotherapy treatment(14). The majority of randomised controlled trials (RCTs) of G-CSF prophylaxis for NHL relate to patients receiving intravenous chemotherapy for high-grade disease.(15) Data reported by the Office of National Statistics data for England in 2004 reported that out of 5172 cases of NHL which could be identified as either high-grade or low-grade approximately 72% were high-grade.(16) Using UK incidence data the mean age of NHL patients (both low grade and high grade) was calculated to be 65 years for men and 68 years for women.(17)

METHODS

Model structure

A mathematical model was constructed using TreeAge Software (TreeAge Software Inc, USA) to estimate the costs and quality adjusted life years (QALYs) accrued by different strategies of G-CSF use. A lifetime horizon was used as an FN episode may impact on patient survival.

The modelling approach conforms to the National Institute for Health and Clinical Excellence (NICE) methods guidance.(18) The model takes the perspective of the UK National Health Service (NHS) and was populated with UK data where possible. A meta-analysis was performed to obtain pooled estimates of effectiveness, EQ-5D utility values were used, and future costs and benefits were discounted at a rate of 3.5% per annum. Willingness-to-pay (WTP) thresholds of £20,000 and £30,000 were used to calculate net monetary benefit (NMB).(18) The base case analysis is for females with the effect of gender examined in a scenario analysis. Several FN risk factors and NHL survival risk factors are included in the modelling and the relationships modelled are shown in Figure 1, and discussed below.

The model structure is shown in Figure 2. For NHL, 6-8 cycles of chemotherapy are usually given.(14) A typical course of CHOP or R-CHOP (CHOP plus rituximab) chemotherapy for NHL in the UK is 6 cycles of 3 weeks each, or 18 weeks in total.(14) Recent studies have shown improvements in both complete remission and survival following reduction of the cycle length of standard 21 day CHOP (CHOP-21) to 14 days (CHOP-14). (19) It is common that primary G-CSFs are administered in combination with CHOP-14. A regimen consisting of 6 chemotherapy cycles of CHOP-21 is modelled here to reflect current UK practice, and in each chemotherapy cycle a patient may or may not experience an FN event.

An FN event may cause chemotherapy dose delays/reductions (i.e. sub-optimal relative dose intensity, RDI) which may affect patient survival. (20) Post-chemotherapy, the model uses a state transition model with a cycle length of 1 year. Life expectancy is estimated using NHL survival data (which is dependent on stage at diagnosis). Patients may die of FN during chemotherapy and from NHL or other causes after chemotherapy. During chemotherapy only deaths due to FN are

considered but post chemotherapy deaths from NHL and other causes are considered.

One and two way sensitivity analyses were undertaken. Probabilistic sensitivity analyses (PSA) were run using 10,000 sets of parameters sampled independently from the parameter distributions. Distributions used were taken or calculated from published sources where available. Further details on choice of distributions are given in the data population section. The appropriateness of 10,000 configurations was tested using jack-knife techniques.(21)

Data Population

Calculating FN risk for patients receiving no prophylaxis
Baseline FN risk, defined as the likelihood of having at least one FN episode over all cycles of chemotherapy in the absence of any G-CSF prophylaxis during treatment, can vary widely amongst patients depending on chemotherapy regimen, patient age, performance status, and other risk factors.(7) The EORTC guidelines show that baseline risk can vary from 11% to 78% for NHL chemotherapy regimens.(7) It has also been established that the risk of an initial FN episode is greatest in chemotherapy cycle 1, with over 50% of initial FN events occurring in the first cycle.(22) (23) The relative risk of an initial FN event in cycles 2 onwards compared with cycle 1 was calculated as 0.2 (95% CI: 0.14 – 0.25) using data from an observational study of 577 NHL patients receiving CHOP chemotherapy. (22) In addition, occurrence of an FN event indicates that a patient is at a higher risk of further FN events in subsequent cycles. The increased relative risk of further FN episodes in a patient with prior episodes was calculated as 9.09 (95% CI 6.19-13.35), using data from a breast cancer study which was the only source found which distinguished between initial and subsequent FN events by cycle.(24) Lognormal distributions fitted to these confidence intervals were used for these FN related relative risks.

For high grade NHL, CHOP and R-CHOP are the most common first-line regimens.(15) For patients with NHL receiving CHOP chemotherapy the reported FN incidence ranges from 17-50%. (25) (26) Lyman et al report a FN hospitalisation rate of 17% for patients receiving CHOP/R-CHOP/CNOP; patients in this study had a median age of 63 years and 8% received G-CSF prophylaxis.(25) Three RCTs in elderly patients receiving CHOP reported that patients in the control arm (not receiving primary G-CSF prophylaxis) had an FN incidence of 37%, 45% and 50% (median age 71-72 in all studies).(10;26;27) The base case analysis in the present study is based on a FN risk level of 17% and a patient age of 63 years. A secondary analysis considers a FN risk level of 45% for a patient age of 72 years.

To inform decision-making for a broad population of patients, we modelled the cost-effectiveness of G-CSF for a range of baseline FN risk values. Our model required the FN risk per cycle, which we calculated from the baseline risk using the information given above, and assuming 6 cycles of chemotherapy. For example, assuming a FN risk of 20%, this was estimated to be a risk of 10% in cycle 1 and a risk of 2% in each

of cycles 2-6. If a patient had an FN episode in cycle 1, this increased the FN risk in each subsequent cycle to 18%. Further details on these calculations are given in a similar cost-effectiveness analysis for breast cancer. (13)

G-CSF efficacy and duration of treatment

A full systematic review of literature relating to G-CSF efficacy was undertaken. The comparative efficacy of the three G-CSFs in reducing FN risk is evaluated using meta-analyses of trials of each G-CSF compared with no primary G-CSF prophylaxis (summarised in Table 1). This included all reported RCTs comparing primary G-CSF prophylaxis versus no primary G-CSF prophylaxis in adult solid tumour and malignant lymphoma patients. This work updated an existing meta-analysis by Kuderer et al (28) and a summary table is provided in the breast cancer cost-effectiveness analysis.(13) The results of the meta-analysis were used in the base-case analysis.

The majority of clinical trials of filgrastim and lenograstim alongside chemotherapy cycles of 3-week duration used approximately 11 injections per cycle, by which point the neutrophil count had generally recovered.(5;29;30) Therefore we have assumed that 11 days' treatment with either lenograstim or filgrastim is consistent with the efficacy evidence reported within the RCTs. To account for the possibility of a shorter duration we have also modelled the use of filgrastim/lenograstim for 6 days and optimistically assumed the same efficacy as for 11 days. A retrospective analysis by Weycker et al showed that the risk of hospitalisation for neutropenia or infection declined with each additional day of filgrastim use, with an odds ratio of 0.81 (95% CI: 0.70, 0.93). Hence our assumption is likely to overestimate efficacy in the 6 day arm.

Mortality rates

The probability of dying through causes other than NHL is assumed to be dependent on age, and is taken from Office for National Statistics data.(31) The model used NHL survival data which was dependent on age, sex, number of years since diagnosis and whether the patient had an RDI level of 85% or greater. Relative survival data from 2000-2004 for Scotland was used because it includes survival rates at 1, 3, 5 and 10 years, by age and sex and by year since diagnosis, and equivalent data could not be identified for England or Wales.(32) It is assumed that the mortality rate is constant in years 2 and 3, years 4 and 5, and in years 6 onwards. Mortality rates are available at age range midpoints and interpolation is used for ages between these points. A limitation of these data is that they relate to all NHL patients, not just those who undergo chemotherapy. It is not clear in which direction this will bias results as the fact that a patient is receiving chemotherapy may indicate a good performance status but it may also indicate advanced disease with an increased risk of mortality.

A study by Kuderer et al analysed 8,871 lymphoma patients hospitalised for FN in the US between 1995 and 2000.(1) The mortality rate from FN for lymphoma patients was 8.9% (95% CI 8.3% to 9.5%) and this is used in the model.

Reduced relative dose intensity (RDI) of chemotherapy due to FN

A high proportion of NHL patients on chemotherapy experience FN with the consequence of impaired chemotherapy delivery.(33) In NHL, reduced RDI is commonly defined as receipt of <90% of the planned chemotherapy dose intensity (either as a result of a reduced dose or a delay between doses).

A retrospective study of 4,522 patients with aggressive NHL treated with CHOP, R-CHOP or CNOP assessed the incidence of and risk factors for reduced RDI.(34) A multivariate analysis identified several independent predictors for reduced RDI, including age older than 60 years, advanced disease stage, poor performance status, and no prophylactic CSF use but found that age was no longer a significant risk factor in patients who received prophylactic CSF. (34)

In the model it is assumed that FN is a risk factor for reduced RDI. A prospective observational study found the proportion of patients with RDI ≤90% was 40.8% in the group without FN and 70.6% in the group with FN; these rates have been used in the model. (33)

Impact of RDI on survival
The relationship between chemotherapy dose intensity and survival is uncertain. However, it is generally considered that a reduction in RDI below the optimum is likely to be detrimental to long-term survival from cancer.(35) In particular, in situations where dose-dense or dose-intense chemotherapy strategies are used reduction in RDI may be detrimental to survival. (7)

A retrospective study of NHL patients by Bosly et al, performed a multivariate Cox regression analysis of factors significantly associated with overall survival in patients receiving CHOP-21 (N=210). (20) This found that average RDI (ARDI) ≤90 vs. >90% was associated with a hazard ratio (HR) for overall survival of 0.48 (95% CI 0.27, 0.84), p-value=0.011. In this study 60 patients (29%) had ARDI ≤90% whilst 150 persons (71%) had ARDI>90%. We note that as this is a retrospective study it may be confounded by the fact that patients who have their dose intensity reduced may be those who are more likely to die due to other factors such as older age and poorer performance status.

The values from this study were used to estimate mortality rates for low and high RDI from the mean age dependent mortality rate as follows:

Mean mortality rate = (probability RDI <90%)*(mortality if RDI <90%)
+ (probability of RDI >=90%)*(mortality if RDI >=90%).

Hence rearranging we get:
Mortality if RDI <90% = mean mortality / (29%+71%*HR), and
Mortality if RDI >=90% = mean mortality*HR / (29%+71%*HR).

As the quality of the data relating FN events to reduced RDI and reduced RDI to survival is of poor quality a sensitivity analysis was performed which assumes that RDI has no effect on survival.

Utility values

Utility values which are dependent on both health state and patient age were used. The average population utilities, categorised by age, have been taken from Kind et al.(36) Each adverse health state (FN, receiving chemotherapy for NHL, relapsed and disease free) is assumed to be associated with a decreased utility for the duration of the event. Each chemotherapy cycle is assumed to last for 3 weeks and the mean length of hospitalisation following an FN event is estimated to be 10.7 days (95% CI: 10.4 to 11.0). (1)

The utility value for the health state "FN" was reported as 0.33 (37) and was converted into a utility multiplier of 0.398 (by dividing by 0.83, the age factor for age 55 years,(36) assuming published utility is for patients aged 55 years). The utility value for the health state "receiving chemotherapy for NHL" was reported as 0.63 with a mean patient age of 72 years and was converted into a utility multiplier of 0.84 (by dividing by 0.75, the age factor for age 72 years). (38) (36) Based on 5 year survival data, it was assumed that in years 1-5 post chemotherapy 41% of patients experience a relapse and 59% of patients are disease free. For years 5 onwards post chemotherapy the disease-free state utility value was assumed for all remaining patients. The utility multiplier for the disease-free state, 0.94, was taken from Hind et al 2007 and the utility value for relapse was assumed to be 0.44, the value for the group with age-adjusted international prognostic index of 2-3 from the Doorduijn study (giving a multiplier of 0.58). (39) (38) Beta distributions were used to model uncertainty in utility values.

Valuation of Costs

Only costs incurred during the time on chemotherapy are included in the model. The unit costs used within the model are detailed in Table 2. It is assumed that G-CSF injections are administered by a district nurse at the patient's home. It is assumed that FN treatment is administered on an inpatient basis. Filgrastim and lenograstim were assumed to be administered as weight based doses at 5mcg/kg/day and details are provided in a similar cost-effectiveness analysis for breast cancer. (13) Since the G-CSF market in the UK is driven by competitive tenders it is common for discounts to be provided on list prices. Therefore various discounted prices were considered in a sensitivity analysis.

The costs of chemotherapy are dependent on the number of chemotherapy cycles received. If a patient dies from an FN event during chemotherapy, no further cycles are given and no further costs incurred. Chemotherapy costs vary depending on the regimen. For simplicity the cost of CHOP is used at £1,931 per cycle.(40) Costs of chemotherapy have been assumed to be independent of RDI.

RESULTS

Results are presented for a baseline FN risk of 17% and a patient age of 63 years which corresponds to a study of patients receiving CHOP/R-CHOP/CNOP

chemotherapy.(41) We calculate the incremental costs and QALYs compared with a strategy of no G-CSF prophylaxis. These are presented alongside the net monetary benefits and incremental cost effectiveness ratio (ICER) in Table 3. We observe that all the strategies involving the once-daily G-CSFs (filgrastim and lenograstim) are never optimal. The ICER for secondary prophylaxis with pegfilgrastim was £7,631 and for primary prophylaxis it was £27,176. The cost effectiveness acceptability curve (CEAC) (42) is shown in Figure 3. With a WTP threshold of £30,000 per QALY primary and secondary prophylaxis with pegfilgrastim each have a probability of being the most cost effective of 0.5. Jack-knife techniques on an example dataset of 10,000 PSA runs showed that the confidence interval around a mean cost per QALY was small (less than £1,000 in all cases).

We also performed an analysis which corresponds to elderly patients receiving CHOP. For this subgroup the analysis used an age of 72 and a FN risk level of 45%.(10;26;27) For this subgroup the ICER for primary prophylaxis with pegfilgrastim was £6,903 whilst secondary prophylaxis with pegfilgrastim was cost saving.

Deterministic one-way sensitivity analysis on baseline FN risk level was performed for a selection of scenarios and results are presented in Figure 4. Results are highly sensitive to baseline FN risk. The base case analysis with a WTP threshold of £20,000 per QALY demonstrated that for a patient with an FN risk level of 8-22% secondary prophylaxis with pegfilgrastim is most cost effective and for patients with higher FN risk levels primary prophylaxis with pegfilgrastim becomes the most cost effective. Using a WTP threshold of £30,000, primary prophylaxis with pegfilgrastim was cost-effective for baseline FN risks greater than 16% and secondary at FN risk of 6-15%.

The scenario analyses performed demonstrate that age at diagnosis, WTP threshold, effect of RDI on survival, sex, and G-CSF price all significantly affect the level of baseline FN risk at which G-CSF prophylaxis becomes cost effective. The scale of the effect these variables can have on the ICER is shown in Figure 4.

DISCUSSION

The cost effectiveness of prophylaxis with the G-CSFs pegfilgrastim, filgrastim and lenograstim is estimated in patients with NHL. Our results indicated that the most cost-effective strategy is dependent on the estimated baseline risk of FN for an individual patient, the cost per QALY threshold, patient age and G-CSF price. It is noted that in all scenarios the most cost-effective strategy was one of primary pegfilgrastim, secondary pegfilgrastim or no G-CSFs and strategies involving 6/11-day filgrastim or lenograstim were dominated.

A sensitivity analysis on age at diagnosis demonstrates that for younger age-groups primary prophylaxis with pegfilgrastim is more likely to be the most cost effective strategy. Since the G-CSF market in the UK is driven by competitive tenders it is common for discounts to be provided on list prices. Including the possible discounting of G-CSFs within the modelling also greatly reduces the FN risk threshold at which primary prophylaxis with pegfilgrastim is cost effective. The overall decision on whether to use G-CSFs will depend on the clinician's assessment of risk factors for a particular patient.

For a particular chemotherapy regimen, the baseline FN risk, and therefore the cost-effectiveness of G-CSF prophylaxis, will vary for individual patients depending on patient risk factors such as performance status, age, etc. A clinician would be assumed to estimate the risk of FN for an individual patient according to factors such as performance status as well as the chemotherapy regimen they were receiving. As age increases, there will be a decrease in remaining expected QALYs but an increase in expected baseline FN risk which impact the cost-effectiveness in opposing directions

The cost effectiveness analysis of G-CSF prophylaxis for breast cancer patients undergoing chemotherapy concluded that a WTP threshold of £30,000 primary prophylaxis with pegfilgrastim was cost effective for patients with an FN risk of greater than 29%.(13) For NHL, G-CSF prophylaxis is cost effective at a lower FN risk level of 16%. As NHL patients often receive treatment with chemotherapy regimens associated with a high risk of febrile neutropenia, it follows that G-CSF prophylaxis may be cost effective for a large proportion of NHL patients.

This study had a number of limitations. Certain assumptions had to be made due to limitations in the data available. For example UK-specific data was not available for all parameter values so data from other countries was used. A statistical analysis relating patient age, performance status and chemotherapy to FN risk was not available but the modelling would be improved if the relationship between these factors was included. The availability of further data reporting FN events with details of chemotherapy cycle number and initial FN events would make the modelling more robust. For example, no NHL-specific data was identified for the increase in FN risk in patients having had an initial FN event, so data from a breast cancer study was used. The retrospective nature of the data linking RDI to survival and the lack of efficacy data for 6 day daily G-CSFs are also limitations.

A published cost-effectiveness analysis which evaluated the cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis found ICERs of between $1,677 and $6,190 per QALY.(43) This model differed in several respects from the model described here: a US perspective was taken, each cycle of chemotherapy was not modelled separately, the risk of FN was assumed the same for secondary prophylaxis and no G-CSFs, and a baseline FN risk of 27.9% was used. Differences in the conclusions of these analyses are due to: the use of different pegfilgrastim efficacy values, different costs and care pathways for different countries, and differences between the structures of the models used.

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TABLES AND FIGURES

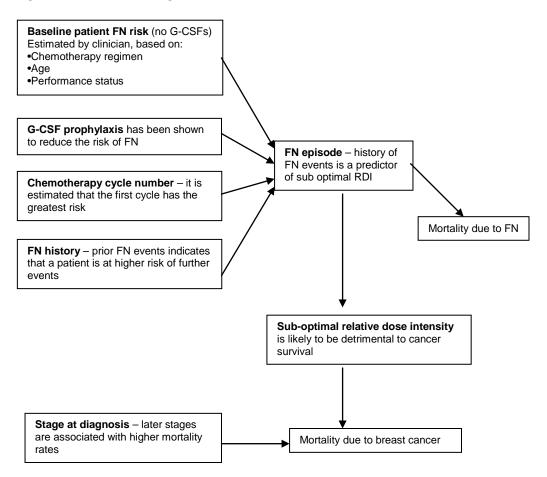**Figure 1: Factors affecting FN risk and survival**

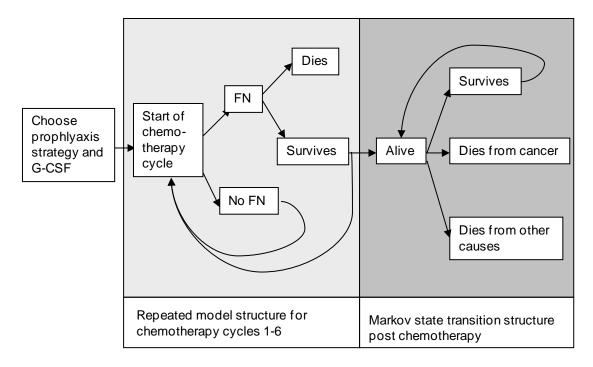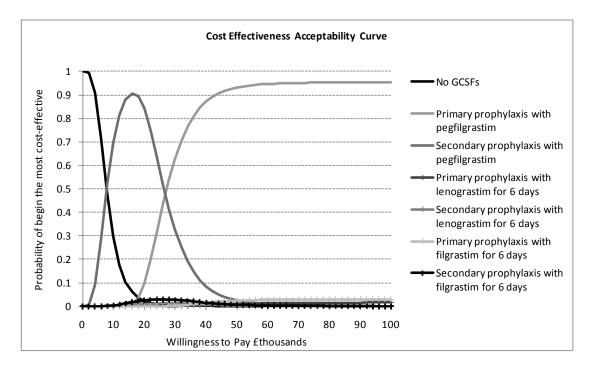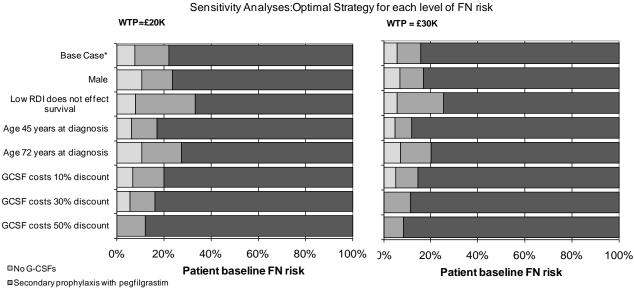**Figure 2: Schematic of the decision analytic model**

Figure 3: Cost Effectiveness Acceptability Curves for base case analysis

(Base Case: CHOP chemotherapy, FN risk level 17%, age 63 years, list price GCSFs)

Figure 4: Sensitivity Analyses: The G-CSF strategy with highest NMB for different levels of baseline FN risk

*Base case is G-CSFs at list price, age 63 years at diagnosis

Figure 5: Tornado diagram for primary prophylaxis with pegfilgrastim compared to

secondary prophylaxis with pegfilgrastim

□ Patient FN risk (no G-CSFs): 0.1 to 0.7
□ Hazard Ratio for survival if low RDI: 0.33 to 1
□ Discount rate applied to drug prices: 0 to 60%
□ Age at diagnosis : 45 to 72
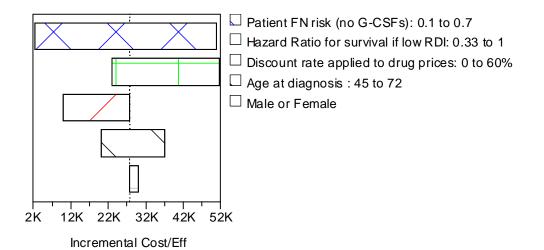□ Male or Female

Table 1: Relative risk of febrile neutropenia incidence with G-CSF prophylaxis

G-CSF prophylaxis	Source	Relative risk of FN compared with no G-CSF prophylaxis (95% CI), p value
Pegfilgrastim	Vogel 2005(6), Balducci 2007(10), Romieu 2007(44), Hecht 2009(45)	0.30 (0.14 to 0.65), p=0.002
Filgrastim (11 day)	Kuderer 2007(28), del Giglio 2008(46)	0.57 (0.48 to 0.69), p<0.00001
Filgrastim (6 day)	Assumed same as 11 day	0.57 (0.48 to 0.69), p<0.00001
Lenograstim (11 day)	Kuderer 2007(28)	0.62 (0.44 to 0.88), p=0.007
Lenograstim (6 day)	Assumed same as 11 day	0.62 (0.44 to 0.88), p=0.007

Table 2: Summary of parameters used in model: deterministic values, distribution used in

PSA, and references

Variable	Value	Distribution	Source
Costs			
Cost of pegfilgrastim per injection	£ 686.24	Assumed fixed	BNF(47)
Cost of filgrastim per injection (weight based dose 5mcg/kg/day)	£ 98.39	Assumed fixed	BNF(47)
Cost of lenograstim per injection (weight based dose 5mcg/kg/day)	£ 111.83	Assumed fixed	BNF(47)
Cost of administrating a G-CSF injection	£ 21.00	Assumed fixed	Curtis 2007(48)
Cost of CHOP chemotherapy per cycle	£ 1931.00	Assumed fixed	Knight et al 2004 (40)
Cost of hospitalisation per day	£ 235.00	Assumed fixed	Curtis 2007(48)
Cost of IV antibiotics during hospitalisation	£ 47.23	Assumed fixed	BNF(47)
Cost of daily investigations (per day of hospitalisation)	£ 9.27	Assumed fixed	Sweetenham et al 1999(49) uplifted to 2007
Cost of once-per-FN investigations (per FN)	£ 47.86	Assumed fixed	Sweetenham et al 1999(49) uplifted to 2007
Average duration of hospitalisation for an FN event in days	10.7	Normal(Mean = 10.7, Std Dev = 0.153)	Kuderer et al 2006(1)
Rate used for discounting costs and QALYs	0.035		NICE reference case(18)
RDI and mortality inputs			
Probability of dying from an FN event	0.089	Normal(Mean = 0.089, Std Dev = 0.003)	Kuderer et al 2006(1)
Probability of low RDI for patients with no FN	40.8%	Normal(Mean=0.41 StdDev=0.04), 95% CI (0.34,0.48)	Pettengell et al 2006 (33)
Probability of low RDI for patients with FN	70.6%	Normal(Mean=0.71 StdDev=0.06), 95% CI (0.58,0.83)	Pettengell et al 2006 (33)
Hazard Ratio for survival if low RDI (<90%)	0.48	Log-normal (mean of logs=--0.7594, sd of logs=0.2895)	Bosly et al 2007(20)

FN risk

Relative risk of an FN event with pegfilgrastim primary prophylaxis vs. no G-CSF	0.30	Log-normal (mean of logs=-1.2820, sd of logs=0.4709)	meta-analysis, Vogel
Relative risk of filgrastim 11 days compared with no G-CSF	0.57	Log-normal (mean of logs=-0.4909, sd of logs=0.0799)	Kuderer et al 2007(28)
Relative risk of lenograstim compared with no G-CSF	0.62	Log-normal (mean of logs=-0.4886, sd of logs=0.1754)	Kuderer et al 2007(28)
Relative risk of an FN event if patient has already had an FN event	9.089	Log-normal (mean of logs=2.1878, sd of logs=0.1961)	Calculated from data in von Minckwitz et al 2008(24)
Relative risk of an FN event in cycles 2-6 compared with cycle 1	0.186	Log-normal (mean of logs=-1.696, sd of logs=0.1533)	Calculated from data in Lyman et al 2003(22)

Utility values and multipliers*

NHL undergoing chemotherapy	0.63	Range 0.54-0.71	Doorduijn et al 2005(38)
NHL undergoing chemotherapy- multiplier	0.84	Beta(33.5,6.4) 95% CI 0.72-0.94	
FN event hospitalisation	0.33	Range 0.24-0.42	Brown et al 2001(50); Brown & Hutton 1998(51)
FN event hospitalisation - multiplier	0.398	Beta(30.7, 46.5) 95% CI 0.29-0.51	
Relapsed NHL	0.44		Doorduijn et al 2005 (38)
Relapsed NHL - multiplier	0.58	Beta(53.7, 38.9)	
Years 1-5 post chemo - multiplier	0.79		
Years 5+ post chemotherapy- multiplier	0.94	Beta(3.44, 0.21)	Hind et al 2007(39)

*Utility multipliers are multiplied by an age-specific average utility value from Kind et al 1998(36)

Table 3: Probabilistic Sensitivity Analyses Results

	Cost (£)	QALYs	Incr. Cost (£)	Incr. QALYs	Incr NMB (£), WTP=£20K	Incr NMB (£), WTP=£30K	ICER*
Base Case Analysis: FN risk level 17%, age 63							
No GCSFs	£ 12,214	6.540	-	-	-	-	
Secondary prophylaxis with lenograstim for 11 days	£ 12,905	6.556	691	0.016	- 378	- 222	dominated
Secondary prophylaxis with lenograstim for 6 days	£ 12,554	6.556	340	0.016	- 27	130	dominated
Secondary prophylaxis with filgrastim for 6 days	£ 12,500	6.558	286	0.018	71	249	dominated
Secondary prophylaxis with filgrastim for 11 days	£ 12,816	6.558	602	0.018	- 245	- 67	dominated
Secondary prophylaxis with pegfilgrastim	£ 12,437	6.569	223	0.029	362	654	£ 7,631
Primary prophylaxis with lenograstim for 11 days	£ 20,647	6.630	8,433	0.089	- 6,646	- 5,752	dominated
Primary prophylaxis with lenograstim for 6 days	£ 16,687	6.630	4,473	0.089	- 2,686	- 1,793	dominated
Primary prophylaxis with filgrastim for 11 days	£ 19,734	6.642	7,519	0.102	- 5,489	- 4,473	dominated
Primary prophylaxis with filgrastim for 6 days	£ 16,172	6.642	3,958	0.102	- 1,927	- 912	dominated
Primary prophylaxis with pegfilgrastim	£ 15,969	6.699	3,755	0.159	- 571	1,021	£ 27,176
Second Example Analysis: Elderly patients - FN risk level 45%, age 72							
No GCSFs	£ 13,970	6.071	-	-	-	-	
Secondary prophylaxis with pegfilgrastim	£ 13,941	6.256	- 29	0.185	3,736	5,590	-£ 155
Primary prophylaxis with pegfilgrastim	£ 16,284	6.596	2,314	0.525	8,181	13,428	£ 6,903

* ICERs are only presented for strategies on the cost effectiveness frontier. The ICER is calculated compared to the next less effective strategy on the cost effectiveness frontier.