Cost-effectiveness analysis of febrile neutropenia (FN) prophylaxis with pegfilgrastim in non-Hodgkin lymphoma (NHL) patients treated with chemotherapy in Spain

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Background

- Febrile neutropenia (FN) is one of the most severe adverse events of chemotherapy(1).
- FN episodes are usually costly(2), can reduce patients' QoL(3), and have a negative impact on the chemotherapy relative dose intensity and consequently on survival(4).
- Prophylaxis with granulocyte-colony stimulating factors (G-CSF) reduces the FN-risk associated with chemotherapy in Non-Hodgkin Lymphoma (NHL) patients(5).
- Pegfilgrastim, which is administered once per cycle, was shown to be more effective at reducing the incidence of FN than daily GCSFs in multiple meta-analysis of RCTs(6,7).
- It is also important to understand whether its use contributes to an efficient use of healthcare resources.

Purpose

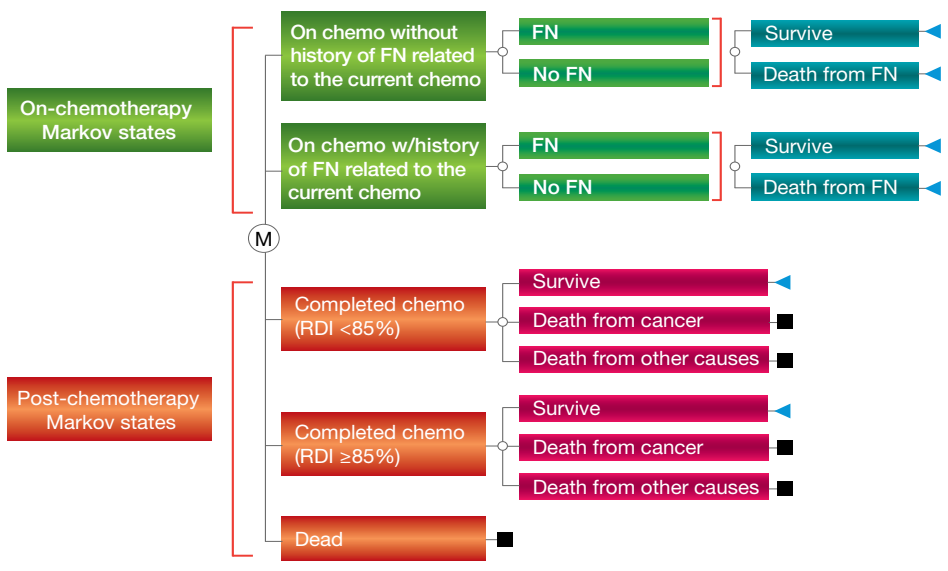
To estimate incremental cost-effectiveness ratios (ICERs) of pegfilgrastim prophylaxis versus other G-CSF prophylaxis strategies or no prophylaxis (no G-CSF use) in NHL patients receiving (R)CHOP-21 chemotherapy from the Spanish National Health System perspective.

Methods

tMODEL DESIGN:

- A 2 stage Markov model (Figure 1) was used to estimate effectiveness and costs over lifetime in NHL patients receiving CHOP-21 or RCHOP-21 regimens.
- Effectiveness was measured in quality-adjusted life years (QALY), a measure of the value of health that combines both length of life and quality of life in a single number.

Figure 1. Model structure



COMPARATORS:

- Pegfilgrastim (Neulasta®) was compared with 11-day and 6-day filgrastim (Neupogen®), and no prophylaxis (no G-CSF use).
- Cost-effectiveness of pegfilgrastim versus other strategies was calculated within primary (PP) and secondary (SP) prophylaxis.
  - PP defined as administration of prophylaxis in all chemotherapy cycles.
  - SP defined as initiating prophylaxis for all remaining cycles after an FN event has occurred.

MODEL INPUTS:

- Population:
  - A cohort of NHL patients (54.6% males) with median age of 69 years (females) and 64 years (males) was analyzed based upon results from a lymphoma registry (RELINF). This registry collected the incidence of lymphoma during 2003 among a population above 9,000,000 inhabitants covered by 54 hospitals in Spain.
  - Patients received CHOP-21 or RCHOP-21 regimens for 6 cycles.
- FN Risk:
  - The 1st cycle FN risk was 19%(8) for patients treated with CHOP-21 and 21%(9) for patients treated with RCHOP-21.
  - FN risk for cycles 2+ was dependent on history of FN:
    - In case of history of FN an increased relative risk of 7.94 was applied(10).
    - In case of no history of FN a reduced relative risk of 0.253 was applied(10).
  - Reduction of FN risk was applied if any prophylaxis strategy was administered, based on efficacy of the prophylaxis strategy *vs.* control group.
- Efficacy of prophylaxis strategies *vs*. control group:
  - For pegfilgrastim, a meta-analysis of four published comparisons of pegfilgrastim *vs*. no primary G-CSF(10,11,12,13) gave a weighted average relative risk for an FN event of 0.249.
  - For filgrastim, the relative risk was 0.614 for 11-day filgrastim(14) and 0.871 for 6-day filgrastim (from linear extrapolation between 4 and 11 days)(15).
- NHL FN-related mortality was 8.9%(16).
- The probability of relative dose intensity (RDI)<85% was estimated from different studies and is shown in Table 1.
- The hazard ratio of survival with a high RDI level (≥85%) as compared to lower level (<85%) in patients with NHL was estimated at 2.083(17).

Table 1. Probability of RDI <85% by age group and prior history of FN(19)

No history of FN		History of FN	
< 65 years	≥ 65 years	< 65 years	≥ 65 years
0.269	0.357	0.368	0.468

- Hospitalization (average 13 days) was considered to be required by 25% of patients suffering a FN event (authors' opinion of Spanish clinical practice).
- Utilities values for patients on chemotherapy, 1st year post-chemo and years 2+ post-chemo were obtained from literature. An utility multiplier was applied in case of hospitalization due to FN.
- The applied annual discount rate for cost and outcomes was 3%(18).
- Resources and cost:
  - One laboratory test (complete blood count and liver and renal function) by cycle was considered.
  - Chemo cost by cycle included the drug cost and the cost of a hospital day care visit for administration.
  - G-CSF self-administration was assumed in 50% of cases (author's opinion).
  - One laboratory test (hemogram and liver and renal function) by cycle was considered.
  - For non-hospitalized patients following a FN event, an outpatient cost for FN event management was also taken into account based on the authors' opinion of Spanish clinical practice.
  - Unit costs (€, 2011) are detailed in Table 2.

Table 2. Unitary costs (€, 2011)

	Cost (€, 2011)
Drug cost	
CHOP-21 (cost per cycle)	€ 95.04(20)
RCHOP-21 (cost per cycle)	€ 1,673.36(20)
Filgrastim 300 µg (Neupogen® exfactory price per pre-filled syringe)	€ 56.99* (20)
Filgrastim 480 µg (Neupogen® exfactory price per pre-filled syringe)	€ 95.44* (20)
Pegfilgrastim 6mg (Neulasta® exfactory price per pre-filled syringe)	€ 965.88(20)
Resources cost	
Hospital day visit for chemotherapy administration	€ 210.50(21)
Visit to nurse for G-CSF administration	€ 15.78(21)
Daily hospital stay	€ 682.27(21)
Laboratory tests	€ 27.75(21)
Outpatient FN event management in non-hospitalized patients	€ 302.10**

*An average cost for filgrastim was calculated (84% patients treated with 300µg and 16% with 480µg)
** Based on detailed resource consumption estimated by authors

Results

- PP with Pegfilgrastim was the most effective therapy.
  - Highest QALY for both CHOP-21 and RCHOP-21 (Table 3).
- Assuming an accepted threshold of €30,000/QALY, PP with pegfilgrastim compared to other PP strategies was cost-effective for both CHOP-21 and RCHOP-21 (Table 4).
- SP with pegfilgrastim vs other SP strategies was also a cost-effective option, being the dominant SP strategy (more effective and less costly) versus 11- and 6-day filgrastim for CHOP-21 and 11-day filgrastim for RCHOP-21 (Table 4).

Table 3. QALYs per prophylactic strategy

	QALYs	
Prophylactic strategy	**CHOP-21**	**RCHOP-21**
No prophylaxis	2.935	2.976
6-day filgrastim PP	2.990	3.023
11-day filgrastim PP	3.090	3.112
Pegfilgrastim PP	3.213	3.220
6-day filgrastim SP	2.953	2.990
11-day filgrastim SP	2.988	3.019
Pegfilgrastim SP	3.040	3.063

Figure 2. Detailed costs of prophylactic strategies in patients receiving CHOP-21 treatment

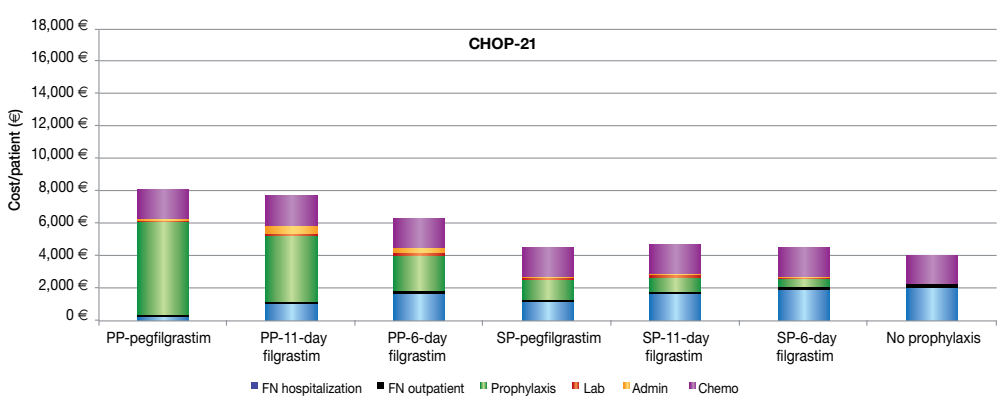
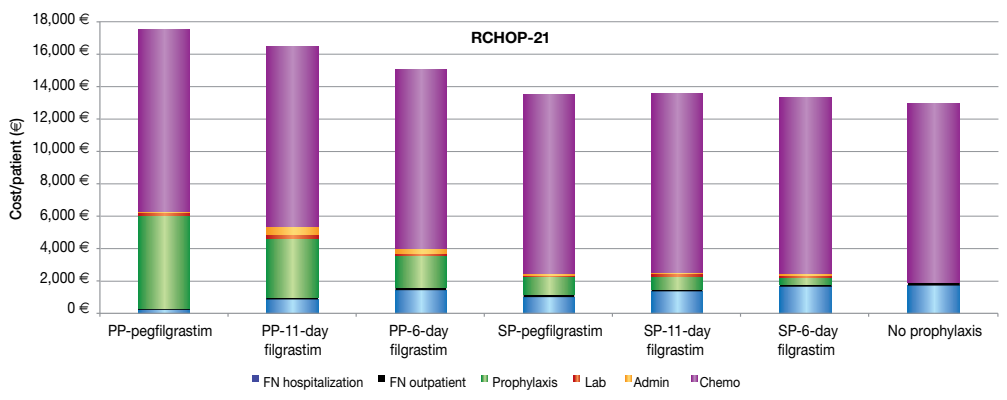


Table 4. Incremental cost-effectiveness ratios (ICER)

Prophylactic strategy	CHOP-21	RCHOP-21
	PP with pegfilgrastim compared to	
No prophylaxis	€ 14,881/QALY	€ 18,898/QALY
6-day filgrastim PP	€ 8,383/QALY	€ 11,433/QALY
11-day filgrastim PP	€ 3,606/QALY	€ 5,895/QALY
	SP with pegfilgrastim compared to	
No prophylaxis	€ 4,806/QALY	€ 7,235/QALY
6-day filgrastim SP	Dominant	€ 1,289/QALY
11-day filgrastim SP	Dominant	Dominant

Note: RCHOP-21 is considered to be the standard of care in aggressive NHL and the majority of NHL patients (should) receive RCHOP-21 therapy.

Figure 3. Detailed costs of prophylactic strategies in patients receiving RCHOP-21 treatment



Limitations

- Due to lack of head to head comparison studies, the efficacy of strategies was compared indirectly through risk reduction over control based on the literature. These efficacy data are consistent with those obtained in published meta-analyses(6,7).
- As drug cost are based on ex factory prices, results could differ depending on discounts applied at the hospital level.
- The patient population in the Spanish registry used in this study was older than the clinical studies from which the model estimates were based, and therefore the model may underestimate FN and related outcomes.

Conclusions

- **Patients receiving PP pegfilgrastim achieve higher number of QALYs than those receiving any other prophylaxis strategy**
- **Pegfilgrastim prophylaxis is an effective and cost-effective treatment for NHL patients for the Spanish NHS.**

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