RESEARCH ARTICLE

Pegfilgrastim Versus Filgrastim for Primary Prophylaxis of Febrile Neutropenia in Patients with non-Hodgkin's Lymphoma: A Cost-Effectiveness Study

Ramin Ravangard[1,2], Najme Bordbar[1,3], Khosro Keshavarz[2], Mehdi Dehghani[4]*

Abstract

Aim: One method to deal with febrile neutropenia is the use of granulocyte colony stimulating factors (G-CSFs). Pegfilgrastim or Filgrastim injection can lead to a reduction in febrile neutropenia and severe neutropenia in patients receiving chemotherapy. This study aimed to compare the cost-effectiveness of using Pegfilgrastim, 3-day Filgrastim and 1-day Filgrastim medication strategies for the primary prophylaxis of febrile neutropenia in patients with relapsed non-Hodgkin's lymphoma after salvage chemotherapy who referred to two referral centers affiliated to Iran, Shiraz University of Medical Sciences in 2014. **Method:** This cost-effectiveness study was conducted on 131 patients with non-Hodgkin's lymphoma. The outcome of the study was the prevention of febrile neutropenia. The cost data were collected from the health payer's perspective for each medication strategy by reviewing the patients' medical records and using expert opinion. The results were presented in terms of the incremental cost-effectiveness ratio (ICER) and the sensitivity analysis was used to assess the robustness of results. In this study, the collected data were analyzed using Excel 2007 and Tree-age 2011. **Results:** The results showed that the degrees of febrile neutropenia prevented by Pegfilgrastim, 3-day Filgrastim and 1-day Filgrastim strategies were 0.97, 0.95 and 0.83, respectively, and the average annual costs of hospitalization per patient were, 5299, 4959 and 5808 PPP$. **Conclusion:** The results showed that while 1-day Filgrastim was absolutely predominant, using the 3-day Filgrastim and Pegfilgrastim strategies were more cost-effective. Therefore, they can be recommended respectively as the first and second treatment priorities in patients with non-Hodgkin's lymphoma after salvage chemotherapy.

Keywords: Non-Hodgkin's lymphoma- febrile neutropenia- pegfilgrastim- filgrastim- cost-effectiveness

Introduction

Cancer is a major cause of health problems, mortalities and disabilities all around the world and its prevalence is increasing every day (Micheli et al., 2003), so that it is expected that the number of new cancer cases rises from 10 million patients in 2000 to 15 million in 2020 (Kanavos, 2006). Therefore, it is obvious that the bulk of efforts of health care systems and system resources are allocated to the cancers (Micheli et al., 2003). Non-Hodgkin's lymphoma is a type of cancers with the origin of the lymphatic system (bone marrow, spleen, thymus, lymph nodes and lymph vessels) . In 2009, a total of 74067 cases of cancer were reported in Iran, among which lymphoma had contained 2.3%(Office of Deputy Minister for Health - Center for Disease Control and Prevention - Cancer Office 2012. Available at: http://vch.iums.ac.ir/uploads/ncr_guideline.pdf). Many patients with non-Hodgkin's lymphoma receive chemotherapy as a part of their treatment (Hoop et al., 2007). Though irrespective of

standard chemotherapy in non-Hodgkin's lymphoma some of patients developed recurrence of disease, thus salvage chemotherapy including ESHAP,IEV and ICE regimen may be effective (Dehghani et al., 2015) However, salvage chemotherapy can cause febrile neutropenia (FN), that can lead to the life-threatening infections and therefore delays in treatment, prolonged hospitalization and unexpected mortality (Crawford et al., 2008; Lyman et al., 2010). The use of the Granulocyte Colony-Stimulating Factors (G-CSFs) is one way to deal with the febrile neutropenia (Groopman et al., 1989).

Therefore, the injection of Filgrastim and Pegfilgrastim can lead to a reduction in the incidence of severe neutropenia in patients who receive salvage chemotherapy (Abrishami and Golshan, 2013).

On the other hand, the cost of patients with cancer is high and the costs of diagnosis and cancer treatment, including visits, medicines, hospitalization and laboratory tests, are the most important direct medical costs of these patients (Khoo et al., 2007). In general, several studies

[1]*Department of Health Services Management,* [2]*Health Human Resource Research Center, School of Management and Medical Information Sciences,* [3]*Student Research Committee,* [4]*Department of Hematology and Medical Oncology, Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. *For Correspondence: Mehdi_dehghani6@yahoo.com*

have been conducted to assess the cost-effectiveness of different Pegfilgrastim and Filgrastim strategies. For example, Sehouli et al. (2010) (Sehouli et al., 2010), Gary H. Lyman et al. (2009) (Lyman et al., 2009b), Derek Weycker and his colleagues (2009) (Weycker et al., 2009), Liu and colleagues (2009) (Liu et al., 2009), Lyman et al. (2009) (Lyman et al., 2009a), and Holmes et al., (2002) (Holmes et al., 2002) in their studies have found out that the use of Pegfilgrastim is more cost effective than non-use of G-CSFs and the use of 6 -day or 11 -day Filgrastim. But the results of the study of Vose et al., (2003) (Vose et al., 2003) showed that the injection of Pegfilgrastim and the daily injections of Filgrastim provided almost the same safety and efficacy.

According to what mentioned above about the non-Hodgkin's lymphoma and its high costs imposed on the patients and the community, and given that the researchers had not found any similar study on the evaluation and comparison of the cost-effectiveness of different strategies of Filgrastim and Pegfilgrastim in the patients with lymphoma in Iran and their searches. The present study aimed to determine and compare the cost-effectiveness of Pegfilgrastim versus 3-day and 1-day Filgrastim as the primary prophylaxis of febrile neutropenia in patients with non-Hodgkin's lymphoma after salvage chemotherapy whoreferred to two referral centers affiliated to Iran, Shiraz University of Medical Sciences in 2014. Therefore, its findings help the managers and policy makers to determine the most cost effective strategy in patients with lymphoma in order to make the proper use of limited resources.

Materials and Methods

This was a cost-effectiveness study on patients with non-Hodgkin's lymphoma with relapse on salvage chemotherapy ESHAP (Etoposide, Cisplatin, Methylprednisolone, high dose Cytosine arabinoside) and IEV(Ifosfomide, Epirubicine, Etoposide) to compare three medication strategies, including Pegfilgrastim) pegylated GCSF 6mg) in the first day after salvage chemotherapy, 3-day Filgrastim (GCSF 5μg/kg) from day 3-5 post chemotherapy and 1-day Filgrastim (GCSF 5μ/kg) at the third day post chemotherapy was given.This is a prophylactic regimen for neutropenic fever that was designed in patients after high dose and salvage chemotherapy for decreasing readmission due to neutropenic fever. The outcome studied in this research was the prevention of febrile neutropenia. The febrile neutropenia was defined if the patients have one peak of temperature above 38.5(^{o}C) orally or sustain fever above 38 (^{o}C) orally with absolute neutrophil count below 1×10^3/dl. Because of prolonged duration of admission and high costs of hospitalization in patients with poor performance status and bone marrow involvement by non-Hodgkin lymphoma, these patients were excluded from this study. The costs, also, were studied from the health payer's perspective; therefore, only the direct medical costs were studied which were collected by reviewing the patients' medical records and using expert opinions. Also, Excel 2007 and Tree-age 2011 were used

for analyzing the collected data.

The study population

This cross-sectional study was carried out on patients with the non-Hodgkin's lymphoma and the age of 19-72 years and on high-dose chemotherapy referred to two referral centers affiliated to Iran, Shiraz University of Medical Sciences in 2014. A sample of 131 patients was determined in the three studied medication strategy groups using the results of a similar study (Grigg et al., 2003), assuming α=5% and β=80. The sample size of each group was selected using stratified sampling proportional to size.

The present study was approved by the ethics committee of Shiraz University of Medical Sciences (Project No. 94-01-07-10067). Also, all patients were free to participate in the study and the informed consent was obtained from all the patients participating in the study and all of them were assured of the confidentiality of their responses.

Cost inputs

In this study, the data of the direct medical costs were collected retrospectively from January 1 to December 31, 2014 through the review of studied patients' medical records. All direct medical costs including the costs of medications used in the hospital ward, the costs of medications injected to prevent febrile neutropenia, the costs of laboratory tests, hospitalization, physician visits, chemotherapy and other costs (containing the costs of radiographies, CT scans, sonographies, ECGs and isolated beds) were identified and calculated. Also, in order to international comparison, the costs were changed into international dollars using the purchasing power parity (PPP) $ exchange rate of 9881.4 Rials per 1 PPP$.

Effectiveness

The effectiveness index in this study was the prevention rate of febrile neutropenia which was determined by a researcher-made checklist used after Pegfilgrastim, 3-day Filgrastim and 1-day Filgrastim injections.

Cost-effectiveness

Based on the results of the previous steps, the FNepisode avoided and cost perFN episode avoided were calculated in each group and their ICERs were estimated using the following formula:

$$ICER = \frac{CostA - CostB}{OutcomeA - OutcomeB}$$

Sensitivity analysis

In this study, the one-way sensitivity analysis was used to assess the effects of the uncertainty of parameters on the results of the study, i.e. the robustness of the results. To do this, the value of each variable changed by 15% and the results were presented by the tornado diagram (Taylor, 2009).

Also, due to the lack of an explicit WTP threshold in Iran, based on the recommendation of the World Health Organization (WHO), one to three times of the Gross Domestic Product (GDP) per capita is used

for the developing countries, which was announced approximately US $ 4670 for Iran in 2014 and its three times was about 14010 dollars. However, for the international comparisons, the latest GDP per capita in Iran on the basis of purchasing power parity (PPP) which was equal to 15090.05 PPP US dollars in 2013 was used.

Results

In this study, 131 patients who were admitted 197 times and 1,007 days to the studied centers were studied in the three medication strategy groups. The first group included 40 patients with 66 times and 310 days of hospitalization treated by Pegfilgrastim. The second group consisted of 44 patients with 65 times and 314 days of hospitalization treated by 3-day Filgrastim, and the third group had 47 patients with 66 times and 383 days of hospitalization with 1-day Filgrastim. The mean age

Figure 2. Tornado Diagram Illustrating the One-Way Sensitivity Analysis Results of Pegfilgrastim versus 3-Day Filgrastim

of the studied patients was 37.77 years and 71% of them were men. The direct costs of diagnosis and treatment services used by each medication strategy group have been shown in Table 1.

Furthermore, the results showed that the amounts of febrile neutropenia prevention were 0.97, 0.95 and 0.83 in the Pegfilgrastim, 3-day Filgrastim, and 1-day Filgrastim strategies, respectively and the average annual costs per hospitalization were, respectively, 5,299, 4,959 and 5,808 US dollars (Table 2). The results of Table 1 and Table 2 show that the use of 3-day Filgrastim compared with 1-day Filgrastim had lower costs and more effectiveness, but compared with Pegfilgrastim, despite having the lower costs, it was less effective. Therefore, among the three medication strategies, 3-day Filgrastim was the most cost-effective strategy and the best next medication strategy was Pegfilgrastim. Also, the 1-day Filgrastim strategy, with more costs and less effectiveness compared to other
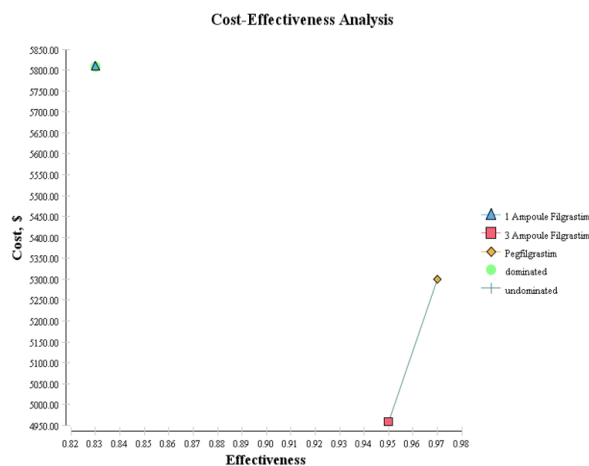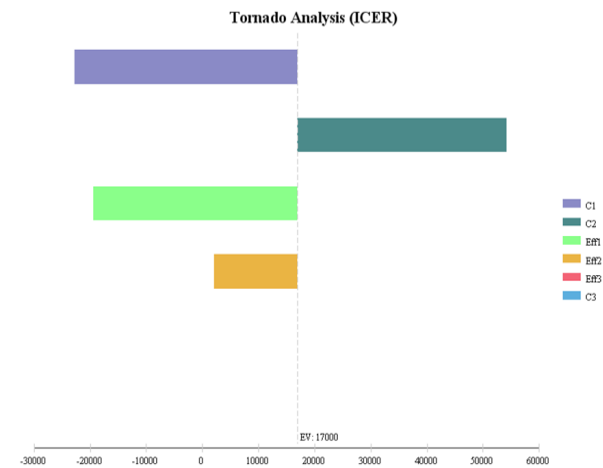

Figure 1. Cost-Effectiveness Analysis of Three Medication Strategies in Patients with Lymphoma Based on The Ratio of Admission without Febrile Neutropenia

Table 1. The Direct Costs of Treating Patients with Lymphoma in Each Medication Strategy in 2014 (PPP$)

Medication Strategy Cost Items	Pegfilgrastim	%	3-day Filgrastim	%	1-day Filgrastim	%
Injected Medication	3,473,192	9.93	1,1051.06	3.43	3,740.36	0.98
Physician Visits	12,125.44	3.47	12,164.18	3.77	14,837.2	3.87
Hospitalization	42,762.15	12.23	42,898.77	13.3	52,325.58	13.65
Chemotherapy	26,132.43	7.47	26,132.43	8.1	26,132.43	6.82
Medication used in the ward	205,891.87	58.86	202,861.21	62.93	251,937.98	65.72
Laboratory Tests	25,340.53	7.24	25,421.49	7.89	31,007.75	8.08
Other Costs	2,755.66	0.78	1,810.86	0.56	3,348.7	0.87
Total Cost	349,740	100.00	322,340	100.00	383,330	100.00
Average Annual Cost Per Hospitalization	5,299$		4,959$		5,808$	

Table 2. The Results of Comparing the Incremental Cost-Effectiveness Ratios of Studied Three Medication Strategies in Patients with Lymphoma Based on Preventing the Febrile Neutropenia (PPP$)

Strategy	cost	Effectiveness	Incremental Costs	Incremental Effectiveness	Incremental Cost-Effectiveness	rank	Subset
3-day Filgrastim	4,959	0.95	0	0	0	1	Dominant
Pegfilgrastim	5,299	0.97	340	0.02	17,000	2	Dominant
1-day Filgrastim	5,808	0.83	509	-0.14	-3635.7	3	Dominated

two strategies, was absolutely dominated.

As it can be seen in Table 2, 1-day Filgrastim and Pegfilgrastim had the minimum and maximum effectiveness, respectively. Also, we found out that 1-day Filgrastim with 5808 PPP$ and 3-day Filgrastim with 4959 PPP$ had, respectively, the highest and lowest average annual costs per hospitalization for the prevention of febrile neutropenia.

Uncertainty analysis

Figure 1 shows the results of one-way sensitivity analysis by a tornado diagram from most to least sensitive strategies. Key parameters included the costs and outcomes were changed by 15%. The results of this analysis showed that the costs of Pegfilgrastim, compared to the other parameters, had the greatest sensitivity on the changes in ICER values.

Discussion

This was the first cost-effectiveness study on patients with non-Hodgkin's lymphoma in Iran which was conducted to investigate three medication strategies from the payers' perspective. In each of the three medication strategies, the majority of the direct medical costs were related to the costs of medications used in the hospital ward; it seems that the high cost of medications in the country is the cause of this result. Also, the results showed that the highest average annual costs per hospitalization was related to the patients who received 1-day Filgrastim, and the next priorities were related to the patients who received Pegfilgrastim and 3-day Filgrastim.

The increases in the average annual costs per hospitalization for the patients who received 1-day Filgrastim were due to the higher costs of medication used in the hospital ward and also the higher costs of hospitalization, laboratory tests and physician visits; which its reason may be the higher febrile neutropenia in patients who received 1-day Filgrastim, and this had increased the number of hospitalization days; therefore, their average annual costs per hospitalization were higher. The results of the present study are confirmed by those of the Weycker and et al.,'s study (2009) (Weycker et al., 2009).

Moreover, the results showed that the effectiveness of Pegfilgrastim, 3-day Filgrastim, and 1-day Filgrastim in the prevention of febrile neutropenia were 0.97, 0.95 and 0.83, respectively. Therefore, the probability of febrile neutropenia in patients treated by Pegfilgrastim was 0.02 less than that in patients treated by 3-day Filgrastim, and also 0.14 less than that in patients treated by 1-day Filgrastim, which are similar to the results of the Liu et al.,'s study (2009) (Liu et al., 2009).

On the other hand, the average annual costs per hospitalization in patients who received 1-day Filgrastim and had more febrile neutropenia was 509 US dollars more than those who received Pegfilgrastim and had less neutropenia. The results of this study were in line with those of the Weycker et al.'s study (2008) (Weycker et al., 2008).

Also, the results showed that the patients who had treated by Pegfilgrastim had the average annual costs of 5299 US dollars per hospitalization for each 0.97 febrile neutropenia prevention. Patients who had treated by 3-day Filgrastim had the average annual costs of 4,959 US dollars per hospitalization for each 0.95 prevention and those treated by 1-day Filgrastim had the average annual costs of 5808 US dollars per hospitalization for each 0.83 prevention of febrile neutropenia.

In addition to the fact that 1-day Filgrastim compared with the two other medication strategies had caused about 12% to 14% more febrile neutropenia and had less effectiveness, it had imposed the annual average costs of 3635.7 PPP$ for each more hospitalization. Therefore, the results showed that 1-day Filgrastim, compared with the two other medication strategy, was absolutely dominated. However, 3-day Filgrastim was the best strategy considering its costs and effectiveness, compared with other options. After that, the best medication strategy was Pegfilgrastim. But considering the fact that its cost effectiveness ratio was less than the country's cost-effectiveness threshold, the use of Pegfilgrastim could be a cost-effective medication strategy. In other words, the Pegfilgrastim medication strategy was not considered as the first treatment priority despite having the highest effectiveness, due to its higher price compared with 3-day Filgrastim. Therefore, with a fixed budget, more patients can be successfully treated with the 3-day Filgrastim medication strategy. In this respect, our results were in line with the results of Gary Lyman et al. (2009) (Lyman et al., 2009b), Lyman and colleagues (2009) (Lyman et al., 2009a), and Holmes et al.,'s (2002) (Holmes et al., 2002) studies.

Finally, the results of sensitivity analyses showed that in case of positive ICER, the results were sensitive to most of the parameters. Therefore, the generalizability of the results decreased. Furthermore, in this case the highest sensitivity was related to Pegfilgrastim costs; so that with changing the costs of Pegfilgrastim, the ICER would become negative. Thus, the use of the threshold was not required, and one of the alternatives was dominant and the other one was dominated. Moreover, the results showed that when the ICER was negative, the study results had low sensitivity to the most of parameters and, therefore, the generalizability of the resultsincreased. It should be noted that in the case of having negative ICER, the highest sensitivity was related to the Pegfilgrastim effectiveness. Given that in this case the ICER became positive, making decision with certainty about the results of the study was not possible and the use of the threshold was required (Ravangard et al., 2014). In the present study, the results were less than the country's cost-effectiveness threshold.

Study limitations

Like other studies, this study had some limitations, such as conducting a cross-sectional study, as well as the incompleteness of some patients' records in terms of data on the medication dosages prescriptions for patients. Also, although the results of this study can be generalized to other medical centers in Iran due to the use of all the three medication strategies for patients with non-Hodgkin's lymphoma , they cannot be generalized to other countries

without considering some items, such as the amount of cost coverage by their insurance organizations, their government's maximum willingness to pay the costs of the most cost-effective treatment strategies, etc.

In conclusion, the results of the present study showed that despite the fact that 3-day Filgrastim was less effective than Pegfilgrastim, it could be considered as the dominant and the best medication strategy due to its lower average annual costs per hospitalization in comparison with Pegfilgrastim. After that, the best medication strategy was Pegfilgrastim because in spite of being the best medication strategy in terms of the prevention of febrile neutropenia, it was not considered as the first priority in the country due to its higher price compared with 3-day Filgrastim. However, the 1-day Filgrastim strategy, compared with the two other strategies, was absolutely dominated. Therefore, the medication strategies of 3-day Filgrastim and Pegfilgrastim can be recommended as the first and second treatment priorities for the patients with lymphoma (Bahadori et al., 2015).

Acknowledgements

Conflict of interest
None to declare.

References

Abrishami F, Golshan A (2013). Frequency of Iron deficiency anemia in girls studying in Mashhad high schools. *Iran J Ped Hematol Oncol*, **3**,143-8.

Bahadori M, Ravangard R, Alimohammadzadeh K, Hosseini SM (2015). Plan and road map for health reform in Iran. *BMJ*, **351**, h4407.

Crawford J, Dale DC, Kuderer NM, et al (2008). Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. *J Natl Compr Canc Netw*, **6**, 109-18.

Definition: Leukemia, lymphoma and myeloma. Available at: http://sylvester.org/cancer/leukemia-lymphoma-and-myeloma/education/definition.

Dehghani M, Haddadi S, Vojdani R (2015). Signs, symptoms and complications of non-hodgkin's lymphoma according to grade and stage in south Iran. *Asian Pac J Cancer Prev*, **16**, 3551-7.

Grigg A, Solal-Celigny P, Hoskin P, et al (2003). Open-label, randomized study of pegfilgrastim vs. daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma. *Leuk Lymphoma*, **44**, 1503-8.

Groopman JE, Molina J-M, Scadden DT (1989). Hematopoietic growth factors. Biology and clinical applications. *N Engl J Med*, **321**, 1449-59.

Holmes F, Jones S, O'shaughnessy J, et al (2002). Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Ann Oncol*, **13**, 903-9.

Hoppe R, Mauch PM, Armitage JON (2007). Hodgkin Lymphoma. Lippincott Williams and Wilkins, Philadelphia, PA.

Kanavos P (2006). The rising burden of cancer in the developing world. *Ann Oncol*, **17**, 15-23.

Khoo K, Colucci R, Hryniuk W, et al (2007). The new wave of cancer drugs, cancer drug access (Part three). Report card on cancer in Canada, Available at: http://www.canceradvocacy.ca/reportcard/2007/Cancer%20Drug%20Access,%20Part%20Three.pdf.

Liu Z, Doan QV, Malin J, et al (2009). The economic value of primary prophylaxis using pegfilgrastim compared with filgrastim in patients with breast cancer in the UK. *Appl Health Econ Health Policy*, **7**, 193-205.

Lyman G, Lalla A, Barron R, et al (2009a). Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. *Curr Med Res Opin*, **25**, 401-11.

Lyman GH, Lalla A, Barron RL, et al (2009b). Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. *Clinical therapeutics*, **31**, 1092-104.

Lyman GH, Michels SL, Reynolds MW, et al (2010). Risk of mortality in patients with cancer who experience febrile neutropenia. *Cancer*, **116**, 5555-63.

Micheli A, Coebergh JW, Mugno E, et al (2003). European health systems and cancer care. *Ann Oncol*, **14**, 41-60.

Ravangard R, Hatam N, Teimourizad A, Jafari A (2014). Factors affecting the technical efficiency of health systems: A case study of Economic Cooperation Organization (ECO) countries (2004-10). *Int J Health Policy Manag*, **3**, 63-69

Sehouli J, Goertz A, Steinle T, et al (2010). Pegfilgrastim vs filgrastim in primary prophylaxis of febrile neutropenia in patients with breast cancer after chemotherapy: a cost-effectiveness analysis for Germany. *Dtsch Med Wochenschr*, **135**, 385-9.

Shillcutt SD, Walker DG, Goodman CA, Mills AJ (2009). Cost effectiveness in low- and middle-income countries: a review of the debates surrounding decision rules. *Pharmacoeconomics*, **27**, 903–17.

Taylor M (2009). What is sensitivity analysis? In What is ...? series. Health Economics. Hayward medical communications, a division of Hayward group Ltd, pp1-8.

Vose JM, Crump M, Lazarus H, et al (2003). Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. *J Clin Oncol*, **21**, 514-9.

Weycker D, Malin J, Edelsberg J, et al (2008). Cost of neutropenic complications of chemotherapy. *Ann Oncol*, **19**, 454-60.

Weycker D, Malin J, Kim J, et al (2009). Risk of hospitalization for neutropenic complications of chemotherapy in patients with primary solid tumors receiving pegfilgrastim or filgrastim prophylaxis: a retrospective cohort study. *Clin Ther*, **31**, 1069-81.

World Bank (2015). PPP conversion factor, private consumption (LCU per international $) US: The World Bank; Available from: http://data.worldbank.org/indicator/PA.NUS.PRVT.PP. (accessed at Febrary 2015).