Cost-Utility Analysis of Recombinant Human Erythropoietin in Anemic Cancer Patients Induced by Chemotherapy in Thailand

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Objective: To conduct a cost-utility analysis on recombinant human erythropoietin (rHuEPO) for treating anemic cancer patients induced by chemotherapy compared to blood transfusion alone under the Thai health care setting.

Materials and Methods: A health care provider's perspective was used to examine relevant costs and outcomes using the Markov model. Cost data were estimated based on the reference price set by the Ministry of Public Health. The effectiveness data were obtained from a systematic review of published literature. The results were presented in terms of incremental cost-effectiveness ratio (ICER) in Thai Baht per Quality Adjusted Life Years (QALYs) gained. A probabilistic sensitivity analysis method was performed.

Results: The ICERs of rHuEPO compared to blood transfusion alone were 3.7 and 2.7 millions Baht per QALY for patients with hemoglobin less than 8 g/dl and 8-9 g/dl, respectively. The rHuEPO required additional resources (more costly) with less benefit compared to blood transfusion for patients with hemoglobin 9-10 g/dl.

Conclusions: The rHuEPO may be cost-ineffective for the treatment of anemia caused by chemotherapy in cancer patients in Thailand.

Keywords: Anemia, Cost-utility analysis, Erythropoietin, Blood transfusion, Cancer, Thailand

Similar to other health care settings, an increase in the number of cancer patients with anemia has been observed in Thailand due to an increase of cancer patients and the use of chemotherapy for treatment of cancers that cause bone marrow suppression[1]. Although blood transfusion is an effective way of increasing the hemoglobin level in anemic patients, several limitations do exist with this approach. These limitations include: a severe shortage of blood donations and the high cost of screening of blood donations. This screening is carried out in order to reduce the residual risk of transmission of bloodborne viruses including hepatitis and human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS)[2].

As a result, an innovation recombinant human erythropoietin (rHuEPO) has been considered as an alternative choice for the treatment of anemia caused by chemotherapy. However, the adoption of rHuEPO has been limited owing to inadequate evidence regarding cost-effectiveness. The findings from a study conducted by the Health Technology Assessment (HTA) program of England suggested that rHuEPO was unlikely to be cost-effective due to the high price of rHuEPO[3]. However, these results may not be applicable to the Thai setting because of the availability of the generic version of rHuEPO, which is much less expensive.

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At present, cost-effectiveness evidence of rHuEPO for the treatment of anemia caused by chemotherapy is not available in Thailand. A primary objective of this study is to assess the value for money of rHuEPO for the treatment of anemia caused by chemotherapy among cancer patients compared to blood transfusion alone in Thailand. Although rHuEPO has been included in the National List of Essential Drugs (NLED) for the treatment of anemia caused by endstage renal disease, it is not included for anemia caused by chemotherapy in cancer patients. The results obtained from this study will be used as an information source for making a decision on whether to include rHuEPO in the NLED for the treatment of anemia due to chemotherapy among cancer patients.

Material and Method

A Markov model was constructed to estimate relevant costs and consequences of rHuEPO treatment compared with blood transfusion alone. The study adopted a health care provider perspective. The results were presented in terms of incremental cost, incremental Quality Adjusted Life Years (QALYs) gained and incremental cost-effectiveness ratio (ICER) in Baht per QALY.

Analyses and model assumption

A schematic diagram of the Markov model is shown in Fig. 1. The model was modified based on the model developed by Wilson et al[3] in order to incorporate treatment guidelines for anemia caused by chemotherapy. These guidelines have been recommended by the Food and Drug Administration of the United State (USFDA)[4], Rodgers et al[5], and the National Health Services of the Northern and Yorkshire[6]. Health states are denoted in the solid line ovals. Six mutually exclusive health states were defined by hemoglobin levels (including death) in the rHuEPO arm and five health states in the blood transfusion arm. An arrow indicates the probability of moving from one state to another. It is determined by transitional probabilistic parameters.

A fixed 4-week cycle length was assigned. The time horizon of the analysis was 7 months, in which the patients received chemotherapy for one week in each six consecutive month period. It was also recommended to continue the treatment for a month following the end of chemotherapy. Costs and QALYs gained were calculated as patients went through the model. Patients were characterized by their hemoglobin level in order to determine which health state to enter. A full dose (150 IU/kg three times weekly) and a half dose of rHuEPO were given when the hemoglobin level was less than 10 g/dl and 10-11 g/dl, respectively. The target result was that the patient's hemoglobin level reached 12 g/dl.

The response to rHuEPO was defined as a 2 g/dl increase in hemoglobin level meaning that patients would move up two states. No response in the first cycle was allowed, which implied no response within the first 4 weeks after treatment. It was assumed that once a patient responded to rHuEPO, he/she would continue to respond to rHuEPO until the treatment was stopped. The response to rHuEPO treatment was assumed to be independent of their hemoglobin level and dose escalation was not considered in this model. Non-response was defined as there being no increase in the hemoglobin level within three cycles (12 weeks), after which patients were treated with blood transfusion and they had to follow the same pathways as those in the blood transfusion arm. Some patients might die anytime at the end of each cycle.
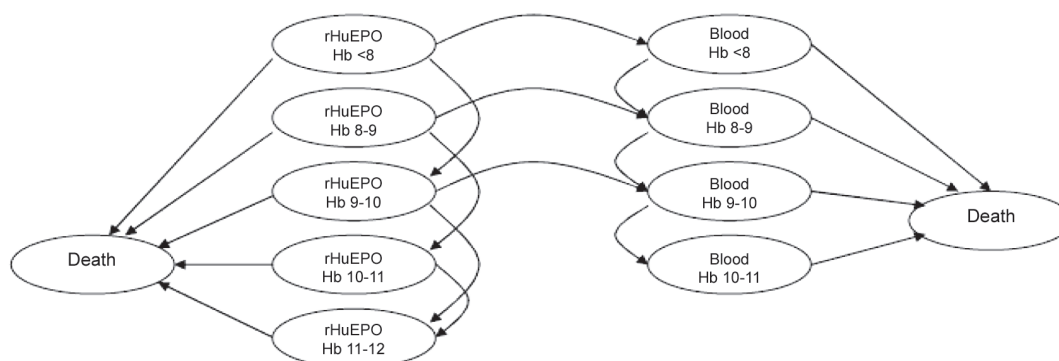

Fig. 1   Schematic diagram of the Markov model

Patients started to receive blood transfusions when their hemoglobin level fell below 10 g/dl. A response was defined as a 1 g/dl increase in a given hemoglobin level. A response was assumed immediately at the end of the cycle but lasting for only one cycle. If the patient was not given a blood transfusion in the following cycle, the patient's hemoglobin level dropped down to the previous level. If another transfusion was given, the patient stayed in that state. Some patients might die anytime at the end of each cycle.

Input parameters

Although the systematic reviews of literature published in several databases, namely Medline, the National Coordinating Centre for Health Technology Assessment (NCCHTA) and the Cochrane library, were carried out, all transitional probabilities and utility parameters used in this study were obtained mainly from a report made by Wilson et al[3]. This report was the most up-to-date and comprehensive study that provided information from a systematic search of both clinical and cost-effectiveness measures. It was found that there was no relationship between the use of rHuEPO and the increase/decrease in a patient's

mortality. All input parameters are shown in Table 1. The probabilities of patients achieving a hemoglobin response in rHuEPO and blood transfusion groups were 0.53 (0.40-0.55) and 1.00, respectively[3]. The probability of dying in each cycle for both the rHuEPO and blood transfusion groups was 0.49 (0.010-0.095)[3].

The utility scores were obtained from a submission of cost effectiveness data of Neo-Recormon Æ (epoetin beta)[3] and epoetin alpha by the Roche and Ortho Biotec Company, respectively[3]. The time trade off (TTO) technique was used to elicit the patient preference on different hemoglobin levels. A higher level of hemoglobin resulted in a higher utility value. The lowest utility value was 0.474 for patients with hemoglobin less than 8 g/dl, and for patients with hemoglobin 8-9 g/dl, the utility value was 0.589. For patients with hemoglobin 9-10 and 10-11 g/dl, the utility were 0.623 and 0.737, respectively. The highest utility value was 0.765 for patients with a hemoglobin level of 11-12 g/dl.

It was assumed that thromboembolic events, which might occur among patients with a high-dose rHuEPO, were not included in the model because rHuEPO was recommended at a lower dose. The target

Table 1. Mean and standard error (SE) of effectiveness input parameters

Parameter	Mean	SE	Parameter distribution	Data source
Transitional probabilities				
Monthly probability of dying	0.49	0.02	Beta	3
Monthly probability of response to rHuEPO in the first cycle	0.00	-	Beta	3
Monthly probability of response to rHuEPO in next cycle	0.53	0.04	Beta	3
Monthly probability of response to blood	1.00	-	Beta	3
Utility parameter				
Utility of patient with hemoglobin less than 8 g/dl	0.474	0.007	Beta	3
Utility of patient with hemoglobin between 8-9 g/dl	0.589	0.026	Beta	3
Utility of patient with hemoglobin between 9-10 g/dl	0.623	0.008	Beta	3
Utility of patient with hemoglobin between 10-11g/dl	0.737	0.045	Beta	3
Utility of patient with hemoglobin between 11-12 g/dl	0.765	0.016	Beta	3
Cost in blood arm				
Monthly cost of Pack Red Cell (PRC) screened by NAT	797	797	Gamma	9
Monthly cost of cross-match testing by gel test	153	153	Gamma	9
Monthly cost of blood administration	716	716	Gamma	9
Monthly cost of laboratory monitoring	100	100	Gamma	**
Cost in rHuEPO arm				
Monthly cost of rHuEPO alfa based on patient 70 kg	38,891	11,565	Gamma	9
Monthly cost of rHuEPO administration	100	100	Gamma	Assumed
Monthly cost of laboratory monitoring	100	100	Gamma	**

* Reference price of multiple brands, Ministry of public health, Thailand 2007
** Assumed to be equal in both arms

for the hemoglobin level was set at 12 g/dl, which would make patients safe from complications[4]. Likewise, the probability of patients being infected with blood borne diseases such as hepatitis B, hepatitis C and HIV/AIDS was not included in the model because the blood products used were assumed to have been screened for blood borne diseases by nucleic amplification testing (NAT). This is very effective in detecting blood borne organisms[7]. In addition, the incubation periods of such infections were much longer than the average life expectancy of the cancer patients. This meant that they would die long before the complications of blood borne infections appeared.

The relevant direct medical care costs were considered using the reference prices from the Ministry of Public Health in the year 2007 and the Civil Servant Medical Benefit Scheme (CSMBS) in the year 2006. The medical costs included the costs of drugs, labor and materials. All costs were converted and reported in 2007 Thai Baht using the consumer price index (CPI). Discounting was not performed since the time horizon was shorter than one year. For international comparison, costs could be converted into international dollars using purchasing power parity (PPP) (US$ exchange rate at 1US$ (2007) = 12.615 Thai Baht[8]). This was not shown in the report.

Uncertainty analysis

A probabilistic sensitivity analysis was performed using a second order Monte Carlo simulation. It was carried out using Microsoft Office Excel 2003 (Microsoft Corp., Redmond, WA). All input parameters were assigned probability distributions according to their attribute to reflect the feasible range of values that each input parameter could attain. Beta-distribution was the choice of distribution for probability and utility parameters, which were bounded zero-one, Gamma-distribution, which ensures positive values, was modeled

for all rates and unit cost parameters. The simulation drew one value from each distribution simultaneously and calculated cost and effectiveness pairs. This process was repeated 1,000 times to provide a range of possible values given the specified probability distribution. The results were expressed as average value of all costs, QALYs and ICER in the Results section[9].

Results

The total costs and QALYs gained from each treatment options, and the incremental costs per QALY gained from providing rHuEPO in comparison to blood transfusion alone, are shown in Table 2. The costs of providing blood transfusions alone were fixed at every hemoglobin levels (each patient needs one unit of blood transfusion for each cycle regardless of their hemoglobin level) while the lower the hemoglobin levels the higher the costs of rHuEPO. As a result, for patients with hemoglobin less than 8 g/dl, 8-9 g/dl and 9-10 g/dl, the incremental costs of providing rHuEPO compared to blood transfusion alone were 116,503, 101,187 and 85,707 Baht, respectively. The incremental QALYs gained for patients with a hemoglobin levels less than 8 g/dl, 8-9 g/dl and 9-10 g/dl were 0.03, 0.04 and -0.01, respectively. The ICERs of rHuEPO were 3.7 and 2.7 millions Baht per QALY for the patients with hemoglobin lelvels less than 8 g/dl and 8-9 g/dl, respectively. Providing rHuEPO was less effective at a higher cost than blood transfusions alone for those patients with hemoglobin levels 9-10 g/dl.

Uncertainty analysis

The results of the probabilistic sensitivity analysis are presented in terms of cost-effectiveness acceptability curves, and are shown in Fig. 2. If policy makers were willing to pay at 100,000 or 300,000 Baht per QALY gained, providing blood transfusions alone was appropriate at all hemoglobin levels. However, at

Table 2. Cost-effectiveness results obtained from the analysis (probabilistic results)

Hemoglobin (g/dl)	rHuEPO		Blood transfusion		Incremental cost (Baht)	Incremental effectiveness (QALYs)	ICER (Baht/QALY)
	Total cost (Baht)	Total effectiveness (QALYs)	Total cost (Baht)	Total effectiveness (QALYs)			
less than 8	127,937	0.31	11,434	0.28	116,503	0.03	3,789,762
8-9	112,621	0.34	11,434	0.30	101,187	0.04	2,746,506
9-10	97,141	0.34	11,434	0.35	85,707	-0.01	dominant
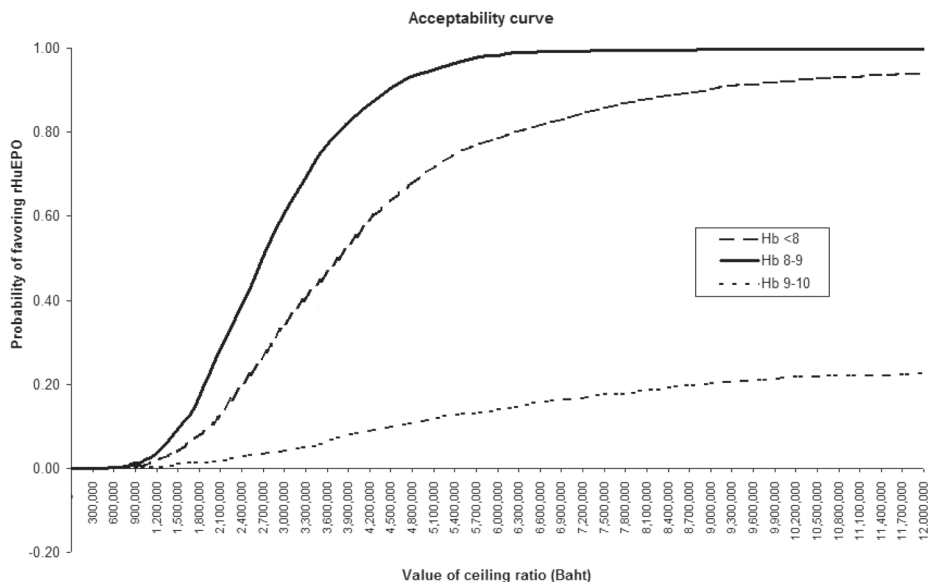
Fig. 2 Cost-effectiveness acceptability curve

the ceiling ratio of 3 million Baht per QALY, providing rHuEPO for patients with a hemoglobin level less than 8 g/dl and 8-9 g/dl was an optimal choice. Providing rHuEPO for patients with hemoglobin 9-10 g/dl was cost-ineffective for every ceiling ratio ranging from 0 to 12 million Baht per QALY.

Discussion

Based on the recommendations made by the Macroeconomics and Health Committee, it was suggested that technology is considered to be cost-effective if its ICER is lower than three times that of the Gross Domestic Product (GDP) per capita[10], This implies a ceiling threshold of 300,000 Baht per QALY in Thailand. The results of this study clearly indicated that rHuEPO is cost-ineffective for treating anemia caused by chemotherapy among cancer patients in Thailand regardless of their initial hemoglobin level. These findings were also in line with the findings from Wilson et al[3]. However, it is noteworthy that some economic evaluation studies that assumed a benefit of rHuEPO concerning the patient's mortality, suggested that rHuEPO was cost-effective[3,11]. As a result, we recommend that a high quality of study or evidence synthesis on whether rHuEPO is beneficial to the patient's mortality should be conducted.

There were several reasons that could explain why rHuEPO appeared to be inferior to blood trans-fusions for treatment of anemia among cancer patients. First, rHuEPO can be very effective in the treatment of anemia if the patients have depletion of serum erythropoietin such as patients with end-stage renal disease. Nevertheless, anemia in cancer is commonly caused by cytokines blunting erythropoietin response or chemotherapy inducing bone marrow suppression or both[12]. The patients tend to have a normal or high blood level of erythropoietin[13]. As a result, cancer patients would gain less benefit from being treated by erythropoietin. Second, there was no linear relationship between hemoglobin levels and the increase of the patient utility[14]. For instance, the utility increases the most for a shift from hemoglobin levels less than 8 g/dl to 8-9 g/dl, while it increases the least for a move from hemoglobin level 10-11 g/dl to 11-12 g/dl. Thus, treating anemia for patients with relatively high hemoglobin levels yields a lower benefit than treating those with relatively low initial hemoglobin levels.

At present, the subcommittee for development of the NLED has decided not to include erythropoietin for the treatment of anemia among cancer patients from the NLED because it proved cost-ineffective and also the recent cancer treatment trials reported that a maximum dose of erythropoietin was associated with decreased survival, especially when rHuEPO was used to maintain hemoglobin at a level higher than 12 g/dl or 13 g/dl[15]. Furthermore, we hope that this study can be

used as an example for those interested in using economic evaluation as a tool for priority setting of health interventions and technology. Using such a tool in decision-making not only makes policy decisions transparent and evidence-based but also increases the use of health care resources more efficiently in the Thai health care setting where the scarcity of health care resources is increasingly causing concerned.

References

1. Attasara P. Hospital-based cancer registry 2005. Bangkok: National Cancer Institute, Department of Medical Services Ministry of Public Health Thailand; 2005.
2. Hall GD. Recombinant human erythropoietin in cancer-treatment related anaemia. London: A submission to the NICE technology appraisal process on behalf of the Royal College of Physicians, Royal College of Radiologists, the Association of Cancer Physicians and the Joint Collegiate Council for Oncology; 2004.
3. Wilson J, Yao G, Raftery J, Bohlius J, Brunskil S l, Sandercock J, et al. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technology Assessment 2007; 11(13). Available from: http://www.hta.ac.uk/fullmono/mon1113.pdf
4. Steinbrook R. Erythropoietin, the FDA, and oncology. N Engl J Med 2007; 356: 2448-51.
5. Rodgers G M, Cella D , Chanan-Khan A, Chesney C, Cleeland C, Coccia P F, et al. Cancer- and treatment-related anemia. Practice guidelines in oncology 200.Available from: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf.
6. NHS Northern and Yorkshire. The use of erythropoietin in the management of cancer related anaemia. London: Regional Drug and Therapeutics Centre; 2002.
7. Lertiendumrong J, Techakehakij W, Pongpirul K, Tangcharoensathien V, Srirattana S. Policy analysis of using nucleic amplification testing for screening blood donor in Thailand. Bangkok: International Health Policy Program; 2007.
8. International Monetary Fund. The world economic outlook database. Washington: International Monetary Fund; 2007.
9. Teerawattananon Y, Mugford M, Tangcharoensathien V. Economic evaluation of palliative management versus peritoneal dialysis and hemodialysis for end-stage renal disease: evidence for coverage decisions in Thailand. Value Health 2007; 10: 61-72.
10. The Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Geneva: World Health Organization; 2002.
11. Martin SC, Gagnon DD, Zhang L, Bokemeyer C, Van Marwijk Kooy M, van Hout B. Cost-utility analysis of survival with epoetin-alfa versus placebo in stage IV breast cancer. Pharmacoeconomics 2003; 21: 1153-69.
12. Dicato M. Anemia in cancer: some pathophysiological aspects. Oncologist 2003; 8(Suppl 1): 19-21.
13. Ozguroglu M, Arun B, DemiN G, Demirelli F, Mandel NM, Buyukunal E, et al. Serum erythropoietin level in anemic cancer patients. Med Oncol 2000; 17: 29-34.
14. Crawford J, Cella D, Cleeland CS, Cremieux PY, Demetri GD, Sarokhan BJ, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer 2002; 95: 888-95.
15. Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. N Engl J Med 2007; 356: 2445-8.

การประเมินต้นทุน-อรรถประโยชน์ของการใช้ยาอีริโทรโพอีตินเพื่อแก้ไขภาวะโลหิตจางที่เกิดจากยาเคมีบำบัดในผู้ป่วยมะเร็งในประเทศไทย

จิราพรรณ เรืองรอง, ยศ ตีระวัฒนานนท์, อุษา ฉายเกล็ดแก้ว

วัตถุประสงค์: เพื่อวิเคราะห์ต้นทุน-อรรถประโยชน์ของการใช้ยาอีริโทรโพอีตินเพื่อแก้ไขภาวะโลหิตจางที่เกิดจากยาเคมีบำบัดในผู้ป่วยมะเร็งเปรียบเทียบกับการให้เลือดเพียงอย่างเดียว

วัสดุและวิธีการ: ต้นทุนและผลลัพธ์ที่เกี่ยวข้องพิจารณาจากมุมมองของผู้ให้บริการ ตัวแปรต้นทุนได้จากอัตราค่าบริการและราคายาอ้างอิงจากกระทรวงสาธารณสุข ข้อมูลตัวแปรด้านประสิทธิภาพได้จากการทบทวนวรรณกรรมอย่างเป็นระบบ แบบจำลองมาร์คอฟและวิธีวิเคราะห์ความไม่แน่นอนแบบความน่าจะเป็น (probabilistic sensitivity analysis) ถูกนำมาใช้สำหรับการวิเคราะห์

ผลการศึกษา: อัตราส่วนต้นทุนประสิทธิผลของการให้อีริโทรโพอีตินเปรียบเทียบกับการให้เลือดเพียงอย่างเดียวมีค่าเท่ากับ 3.7 และ 2.7 ล้านบาทต่อปีสุขภาวะ ในผู้ป่วยที่มีระดับฮีโมโกลบินต่ำกว่า 8 กรัมต่อเดซิลิตรและระหว่าง 8-9 กรัมต่อเดซิลิตร ตามลำดับ สำหรับผู้ป่วยที่มีระดับฮีโมโกลบินระหว่าง 9-10 กรัมต่อเดซิลิตร ต้องใช้งบประมาณที่สูงกว่าแต่ให้ปีสุขภาวะที่น้อยกว่าการให้เลือด

สรุป: การให้อีริโทรโพอีตินอาจไม่คุ้มค่าสำหรับการแก้ไขภาวะโลหิตจางที่เกิดจากยาเคมีบำบัดในผู้ป่วยมะเร็งในประเทศไทยเมื่อเปรียบเทียบกับการให้เลือดเพียงอย่างเดียว