Routine once-weekly darbepoetin alfa administration is cost-effective in lung cancer patients with chemotherapy-induced anemia: a Markov analysis

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of recombinant human erythropoietin (RHE) for the treatment of chemotherapy-induced anaemia in patients with lung cancer (LC). RHE was administered when the haemoglobin (Hb) level fell below 11 g/dL. The regimen was darbepoetin alpha 150 microg once a week, or twice this dose if the Hb level did not rise by at least one point after 4 weeks of treatment. RHE was withdrawn when the Hb level reached 14 g/dL or 4 weeks after the end of chemotherapy, whatever the Hb level.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who had a histologic or cytologic diagnosis of LC and received chemotherapy.

Setting
The setting was a hospital. The economic study was carried out in France.

Dates to which data relate
The effectiveness and resource use data were gathered from October 2002 to March 2003 for the control group (no RHE) and from April to September 2003 for the intervention group (RHE). The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that included in the effectiveness study.

Study sample
Power calculations were not reported. Two consecutive cohorts of patients receiving chemotherapy for LC were retrospectively identified. The first cohort included all patients who had their first chemotherapy cycle between 1 October 2002 and 31 March 2003 and who never received RHE. The second cohort included all patients who had their first chemotherapy cycle between 1 April and 30 September 2003 and who routinely received RHE. The study sample comprised a total of 183 patients, 89 (64 men) of which were included in the control group and 94 (69 men) in the RHE
The mean age was 63 (+/- 11) years (age range: 38 to 85) in the control group and 64 (+/- 11.1) years (age range: 37 to 88) in the RHE group.

Study design
This was a retrospective comparative study with an historical control that was carried out at a single centre. The two groups of patients were evaluated in two different periods. Follow-up lasted for 1 month after the last chemotherapy cycle. No patient appears to have been lost to the follow-up assessment.

Analysis of effectiveness
All patients included in the initial study sample were considered in the effectiveness analysis. The outcome measures used were:

- the proportions of anaemic patients (defined as an Hb level < 11 g/dL),
- the prevalence of anaemia,
- use of red cell units,
- the proportion of patients who had at least one weekly injection of RHE, and
- changes in the Hb level according to anaemic status at the outset of treatment.

The study groups were generally comparable at baseline in terms of their clinical and demographic factors. The exception was the proportion of patients receiving cisplatin-based chemotherapy, which was higher in the RHE group (85.6% versus 92.4%; p<0.01).

Effectiveness results
Before chemotherapy, the proportion of anaemic patients (Hb < 11 g/dL) was 30.7% in the group receiving RHE and 33.6% in the group not receiving RHE. The mean Hb levels were 13.2 (+/- 1.7) g/dL (RHE group) and 12.7 (+/- 1.9) g/dl (non RHE group), respectively, (p non significant).

The prevalence of anaemia increased with the number of cycles of first-line chemotherapy in the two groups. Among patients who received 6 cycles of first-line chemotherapy, 70% in the RHE group and 73.3% in the non RHE group were anaemic. During second-line chemotherapy, the mean prevalence of anaemia was 33% during the first 3 cycles, then 10% during subsequent cycles.

The use of RHE significantly reduced the proportion of patients needing transfusions (from 33.6 to 19.1%; p<0.05) and the number of red cell units used by transfusion (from 2.97 +/- 1.47 to 2.11 +/- 0.47; p<0.01).

The red cell units were mainly transfused during first-line treatment (72% in the non RHE group and 92% in the RHE group).

In the RHE group, 46.8% of patients had at least one weekly injection of RHE (mean 7.5 +/- 4.2; range: 1 to 9).

In terms of the change in Hb level according to anaemic status at the outset of treatment, the mean Hb in anaemic patients was 9.1 (+/- 0.72) g/dL in the non RHE group and 9.7 (+/- 0.91) g/dL in the RHE group, (p<0.007). The corresponding values in non anaemic patients were 12.6 (+/- 0.71) g/dL (non RHE group) and 13.3 (+/- 1.29) g/dL (RHE group), (p<0.01).

Clinical conclusions
The effectiveness analysis showed that RHE yielded a significantly higher mean Hb level in patients undergoing chemotherapy for LC. The effectiveness results were used to populate the decision model (distribution of patients in the
four health states) and estimate transition probabilities (RHE versus no RHE).

Modelling
A Markov model was constructed to simulate the transition of patients between four exhaustive and mutually exclusive states based on Hb levels. These health states were State An (never-transfused anaemic), State noAnoT (non anaemic, non transfused), State AT (transfused anaemic) and State noAT (transfused non anaemic). Before each chemotherapy cycle, patients were distributed between the different health states according to the initial probability of being anaemic and, hence, the probability of being non anaemic. Twelve cycles were run and the cycle length appears to have been 3 weeks. A graphical representation of the model was provided. The model was populated with data derived from the sample of patients identified at the authors’ institution.

Measure of benefits used in the economic analysis
Since several studies had shown that the haemoglobin level correlated well with quality of life, independently of tumour stage and treatment response, the summary benefit measure was calculated on the basis of an Hb value of 11 g/dL as the reference for efficacy. The utility attributed to each health state was the difference (positive or negative) between this reference level and the mean Hb level for patients in the relevant health state.

Direct costs
The analysis of the costs was undertaken from the perspective of the health care provider. It included the direct costs associated with the medical treatment of patients and transportation. A detailed breakdown of the costs was not provided. The costs associated with transfusion-related viral infections were not considered, owing to the short life expectancy of the patients considered in the study. The cost of bacterial complications related to transfusions and the adverse effects of RHE were not included because of the rarity of these events. The unit costs were not presented separately from the quantities of resources used. Resource use was estimated using data derived from the sample of patients included in the effectiveness analysis. The costs came from national unit cost scales and drug purchase prices. Discounting was not relevant as the costs were incurred during a short timeframe. The price year was not reported.

Statistical analysis of costs
The costs were presented as mean values with standard deviations. Conventional statistical test were run to assess whether the cost-differences were statistically significant.

Indirect Costs
The indirect costs were not considered in the economic analysis.

Currency
US dollars ($).

Sensitivity analysis
Several univariate sensitivity analyses were carried out. These tested the robustness of the model results to variations in the costs of transfusion and RHE administration, the initial probability of anaemia in the study population, the reference Hb level, and the mode of RHE administration. Alternative data were obtained from published studies.

Estimated benefits used in the economic analysis
The simulation of the Markov model for 12 cycles led to mean Hb values of 13 (+/- 0.5) g/dL for the RHE group and 11.9 (+/- 1) g/dL for the no RHE group, (p<0.001).
Cost results
Using the Markov model simulation, the expected costs were $1,732 (+/- 897) for the RHE group and $996 (+/- 643) for the no RHE group, (p<0.01).

Synthesis of costs and benefits
Average cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative strategies. With an Hb level of 11 g/dL as the cut-off for efficacy, the cost-effectiveness ratio was 7.02 for the RHE strategy and 9.04 for the no RHE strategy.

The sensitivity analysis showed that RHE remained the preferred strategy (lower average cost-effectiveness ratio) under most of the alternative scenarios examined, as long as the cost of transfusion exceeded $500 and the prevalence of anaemia before treatment exceeded 10%.

The two strategies were economically equivalent when the cost of RHE was reduced by 52%.

Authors' conclusions
The use of recombinant human erythropoietin (RHE) for the treatment of chemotherapy-induced anaemia in patients with lung cancer (LC) was cost-effective since it reduced both the total number of transfusions and the total number of red cell units transfused. It also increased the mean haemoglobin (Hb) level.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear as the conventional strategy of no RHE was compared with the routine use of RHE. Methods of RHE administration and dosage were given. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were estimated through a comparison of a retrospective group and an historical control group. This design was adopted since the new intervention and the comparator were implemented in two different time periods. As the two groups of patients were not assessed concurrently, factors other than the study interventions might have affected the results of the analysis. Further, the retrospective nature of the study and the lack of random allocation of the patients to the study groups represent two important limitations to the validity of the analysis. Consequently, the potential impact of selection bias and confounding factors cannot be ruled out. The baseline comparability of the study groups and the fact that no patient was lost to follow-up represent advantages of the analysis. However, a further limitation of the analysis was the fact that evidence came from a single institution, which might not be representative of the general population of patients considered in the study. The inclusion of consecutive patients improves the robustness of the comparison. No formal justification for the size of the sample was provided. These issues should be considered when assessing the internal validity of the analysis.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It will not be comparable with the benefits of other health care interventions. The impact of the intervention on quality of life was implicitly evaluated in that the authors stated that published studies had shown that variations in Hb levels were correlated with quality of life.

Validity of estimate of costs
Limited information on the cost analysis was reported. The authors did not provide a clear breakdown of the cost items, although a justification was given for the exclusion of some cost categories. The source of the data was reported only for some items. The unit costs were not presented separately from the quantities of resources used, which limits the possibility of replicating the analysis in other settings. Resource use reflected actual treatment patterns at the authors’ institution. Statistical analyses of the costs were performed, and the impact of changing key cost estimates was
investigated in the sensitivity analysis. The price year was not given, thus hampering reflation exercises in other time periods.

Other issues
The authors compared their results with those from other studies that examined both the costs and effectiveness of RHE. The findings of these other studies were different, mainly because of a different baseline population, and had shown that RHE was not cost-effective. The issue of the generalisability of the study results to other settings was implicitly addressed by running several sensitivity analyses; this enhances the external validity of the study. The authors noted some limitations of their analysis. For example, the exclusion of some categories of costs and the lack of routine serum iron assay and iron supplementation, which might have resulted in the over-prescription of RHE. In addition, the approach used to calculate the cost-effectiveness ratios was unclear, and an average rather than an incremental analysis was performed.

Implications of the study
The study results appear to support the use of RHE for the treatment of chemotherapy-induced anaemia in patients with LC. The authors pointed out "further trials are warranted, notably focusing on iron replacement therapy, tumor response/progression, and survival".

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Other publications of related interest


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