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## Original Paper

# Economic Analysis of the Use of Recombinant Human Granulocyte Colony Stimulating Factor in Autologous Bone Marrow Transplantation

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**The aim of this study was to assess the economic impact of the use of granulocyte colony stimulating factor (RHu-G-CSF) in patients treated by autologous bone marrow transplantation (ABMT) for lymphomas. Demographic, clinical and economic data were collected retrospectively from a random sample of 55 patients in four French centres who underwent ABMT (usual care) without or with administration of RHu-G-CSF over a period of 100 days post-ABMT. The patients treated with RHu-G-CSF had a shorter period of infection, neutropenia and severe neutropenia ($P < 0.05$) when compared with usual care recipients. Compared to usual care, the use of G-CSF was associated with a 3% reduction in total cost of care for ABMT over 100 days post-ABMT or US$1316, including RHu-G-CSF cost. This cost reduction was mainly due to a reduced length of stay in hospital and fewer laboratory tests. Copyright © 1996 Elsevier Science Ltd**

**Key words: cost, RHu-G-CSF, cancer, bone marrow transplant**
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## INTRODUCTION

AUTOLOGOUS BONE marrow transplantation (ABMT) is the only curative procedure for patients with recurrent lymphoma. It is also widely used in the treatment of Hodgkin's disease and in a variety of leukaemias [1]. In France, over 1300 ABMT were performed in 1992 [2]. ABMT has become a more viable treatment with the use of G-CSF which stimulates immune cell colonies [3] and consequently reduces the length of recovery time following ABMT. The clinical benefit of G-CSF in ABMT patients has been proven through a number of randomised clinical trials in various types of lymphomas [4–11]. However, early survival and relapse rates have not been improved in patients who received G-CSF [11]. In addition, the long term clinical benefit of G-CSF in larger patient groups is the focus of on-going research [12].

The use of G-CSF in ABMT is an expensive procedure which may threaten hospital budgets at a time of increasing cost containment. However, it has been reported to decrease the rate of infections and may decrease direct medical costs through reduction of length of hospitalisation and antibiotic utilisation [10, 13–17]. The objective of our study was to compare health care utilisation and costs resulting from the use of RHu-G-CSF compared to no RHu-G-CSF (usual care) in patients undergoing ABMT.

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## PATIENTS AND METHODS

*Patients*

Patients ($n = 55$) were observed in four haematology centres in France. They were included on the basis of their underlying lymphoma (Hodgkin's lymphoma, non-Hodgkin's lymphoma [NHL], leukaemia) and the lack of previous involvement in clinical trials. Patients who had received RHu-G-CSF and patients who participated in clinical trials in the past year were excluded from the analysis. Patients were selected at random from the hospital registry.

*Study design*

The study design was a retrospective cohort patient chart analysis. To control selection bias, patients were matched according to tumour and age at inclusion. Total follow-up period was 100 days from the day of ABMT. Economic and clinical data were collected retrospectively from patients' charts by blinded investigators using a standardised case report form (CRF). Clinical study endpoints were incidence of documented infections, and incidence and duration of neutropenia, anaemia and thrombocytopenia. Resource utilisation data were collected for the transplantation (preparation

for and performance of the surgery) and for 100 days of follow-up. Data were collected as units of health care utilisation for inpatient stays (length of stay, type of ward, utilisation of antibiotic and RHu-G-CSF, chemotherapy, blood products and laboratory tests) expressed in days or incidence. Outpatient data were unavailable due to the structure of patient records in France.

*Economic analysis*

The economic analysis was based on the French hospital perspective. Applying costs to units of health care resources in the hospital setting in France relies on a combination of per day estimates and standard costs for specific services and procedures. In this context, the following methodology was developed. The weighted average per day obtained from a sample of 11 hospitals in France was used for "standard days", i.e. no change in the intensity of care related to the intervention. When an intervention had a clear impact on the amount of care during hospitalisation, a distinction was made between the components of care which were not affected by the intervention. Hence, costs were applied to independent components using a breakdown of the estimate per day for overheads, hotel (room, food, laundry) basic care (personnel, small equipment) and basic drug treatment, excluding antibiotics and chemotherapy. For dependent components (antibiotics, chemotherapy and blood products), an average cost was deducted from the standard per day and their observed utilisation in the cohort was costed using a standard cost per day (tariff list multiplied by number of days utilisation). This approach reduced overestimates due to double counting.

The analytical framework of the economic analysis was a cost minimisation approach. Average total costs and 95% confidence intervals for each item (inpatient stay or procedure) are expressed in 1993 US$ excluding taxes. Average total cost for each strategy (RHu-G-CSF or usual care) was determined from the sum of the following components: (1) costs of standard days of hospitalisation multiplied by the number of days when basic care applies, (2) cost of the independent component of inpatient stay multiplied by the number of days when specific care applies, (3) cost of specific procedures when specific care applies.

A sensitivity analysis was performed to test the robustness of the economic findings by varying the following costs: (1) inpatient hospitalisation per day of haematology wards in general hospitals and in anticancer centres, (2) per day of internal medicine ward in general hospitals.

*Statistical analysis*

Statistical testing was performed on demographics, clinical and resource utilisation data. Testing methods were based on a level of significance of 5%. Categorical data were expressed in terms of percentage and were compared using a chi-squared test. Numerical data were expressed as mean and standard deviation (S.D.) and compared using non-parametric testing. Costs were reported as the average per patient for the 100-day follow-up period.

## RESULTS

The demographic and clinical baseline data analyses (Table 1) show comparable profiles between RHu-G-CSF and usual care groups. Average age ranged from 36.5 to 41.3 years. Types of tumour were very similar with non-Hodgkin's lymphomas predominant (41.4 and 42.3%, respectively). ABMT therapy was balanced across groups with a majority of patients receiving only chemotherapy.

*Table 1. Demographic and baseline clinical data*

| | ABMT with RHu-G-CSF $n = 29$ | ABMT without RHu-G-CSF $n = 26$ |
|---|---|---|
| Observation period | | |
| Age ($n \pm$ S.D.) | 36.5 ± 12.4 | 41.3 ± 11.7 |
| Sex (% male) | 48.3 | 55.4 |
| Weight ($n \pm$ S.D.) (kg) | 67.1 ± 11.1 | 67.2 ± 14.4 |
| Type of lymphoma (%) | | |
| Hodgkin's lymphoma | 6.9 | 7.7 |
| Non-Hodgkin's lymphoma | 41.4 | 42.3 |
| Lymphoma/leukaemia | 13.8 | 11.5 |
| Myeloma | 0 | 3.8 |
| Others | 37.9 | 34.6 |
| Type of intervention (%) | | |
| Chemotherapy | 58.6 | 65.4 |
| Chemotherapy and radiology | 41.4 | 34.6 |

No significant difference was seen between groups.

The clinical data over a follow-up of 100 days post ABMT (Table 2) shows a significant reduction in the duration (5.6% versus 7.8%, $P < 0.05$) of infections in the RHu-G-CSF group. A significant reduction in duration of moderate neutropenia (20.3% versus 29.6%, $P < 0.05$) and severe neutropenia (15.8% versus 21.9%, $P < 0.05$) for patients who received RHu-G-CSF was also seen. While the incidence of anaemia was slightly but not significantly higher in the RHu-G-CSF group compared to usual care (62.1% versus 53.8%, not significant), the rate of mucositis was significantly lower in the RHu-G-CSF group compared to usual care (61.5% versus 87.0%, $P < 0.05$).

In terms of health care utilisation (Table 3), a slightly shorter duration of hospitalisation post-ABMT was observed for the RHu-G-CSF group (4 days, $P < 0.05$) and during the 100 days follow-up period (2.2 days, non-significant). RHu-G-CSF was used at an average daily dose of 6.2 μg/kg. The length of use of RHu-G-CSF (16.4 days) was shorter than the recommended course (20 days). Hospital antibiotics were administered over a slightly longer period in the usual care group (28.3 days versus 24.0 days, not significant). The number of units transfused (red blood cells, platelets) were similar in both groups.

Table 4 indicates the average total cost of care per patient in 1993 US$, using an exchange rate of 5.5 with FF, including the 100-day follow-up period. Overall, the cost of care ranges from US$43341 for the RHu-G-CSF treatment to US$44656 with usual care leading to a potential cost reduction of US$1315, including the cost of RHu-G-CSF. When cost structure was considered, cost reduction was mainly due to shorter length of hospital stay and less initial and post-ABMT hospitalisation days. However, the use of RHu-G-CSF implies additional costs for drugs (RHu-G-CSF, antibiotics) and blood products.

## DISCUSSION

To our knowledge, this study represents one of the largest cohort observations analysing the economic outcomes of RHu-G-CSF use in ABMT. The data reported here indicate

*Table 2. Clinical outcome*

| | ABMT with RHu-G-CSF $n = 29$ | ABMT without RHu-G-CSF $n = 26$ |
|---|---|---|
| Incidence of infection (%) | 86.2 | 100 |
| Duration of infection (days) | 5.6 ± 4.5* | 7.8 ± 6.1 |
| Incidence of neutropenia (%) | 100 | 100 |
| Duration of neutropenia (days) | 20.3 ± 15.6* | 29.6 ± 19.1 |
| Incidence of severe neutropenia (%) | 100 | 96.2 |
| Duration of severe neutropenia (days) | 15.8 ± 6.9* | 21.9 ± 10.3 |
| Incidence of anaemia (%) | 62.1 | 53.8 |
| Incidence of thrombocytopenia (%) | 100 | 100 |
| Incidence of mucositis (%) | 61.5* | 87.0 |

*$P < 0.05$.

*Table 3. Health care utilisation patterns*

| | ABMT with RHu-G-CSF $n = 29$ | ABMT without RHu-G-CSF $n = 26$ |
|---|---|---|
| Initial hospitalisation (days) | 3.3 ± 2.3 | 4.3 ± 3.9 |
| Hospitalisation for ABMT (days) | 30.9 ± 7.2* | 34.9 ± 8.1 |
| Days in sterile unit | 21.9 ± 9.6 | 23.1 ± 10.4 |
| Hospitalisation up to 100 days (days) | 2.9 ± 4.6 | 5.1 ± 10.3 |
| Use of RHu-G-CSF | | |
| Average daily dose (μg) | 421.1 ± 194.3 | — |
| Route of administration (i.v.) (%) | 96.6 | — |
| Length of use (days) | 16.4 ± 6.0 | — |
| Use of antibiotics (days) | 24.0 ± 8.5 | 28.3 ± 8.0 |
| Red blood cell transfusion (units) | 6.1 ± 3.6 | 7.7 ± 3.9 |
| Platelet transfusion (units) | 47.8 ± 45.6 | 44.1 ± 43.1 |

*$P < 0.05$.

*Table 4. Total cost of care per patient per 100 days (1993 US$)*

| | ABMT with RHu-G-CSF $n = 29$ | ABMT without RHu-G-CSF $n = 26$ | Increment (with RHu-G-CSF – without RHu-G-CSF) |
|---|---|---|---|
| Initial hospitalisation | 2810 | 3627 | −817 |
| RHu-G-CSF | 3131 | — | 3131 |
| Hospital stay | 24560 | 26920 | −2360 |
| Chemotherapy | 704 | 522 | 182 |
| Antibiotics | 1954 | 1985 | −31 |
| Other drugs | 156 | 156 | 0 |
| Blood products | 4722 | 4349 | 373 |
| Parenteral nutrition | 153 | 271 | −118 |
| Laboratory test | 1905 | 2230 | −325 |
| Post ABMT hospitalisation | 3243 | 4594 | −1351 |
| Total cost | 43341 | 44656 | −1315 |

that the use of RHu-G-CSF is associated with potential cost reductions which represent 10% of the total cost for ABMT. Including cost of RHu-G-CSF, cost reductions amounted to US$1315 per patient. These findings are consistent with a previous study [11] reporting a significant reduction in median time in hospital by 11 to 15 days. A recent study, performed in a similar French setting with 16 patients, showed similar findings [17].

The data presented here should be considered in light of the methodological limitations of the study design.

Primarily, the sample may be biased in terms of representativeness. The centres included in the analysis are not fully representative of ABMT practice in France. However, sensitivity analysis based on extreme per day estimates indicated the relative robustness of our findings. More importantly, the study was based on non-randomised retrospective observational cohorts that may have led to selection bias. Nevertheless, this approach is frequently used in economic evaluation in oncology [18], and our matched-pair inclusion of patients should balance the groups in terms of basic demographic and clinical terms. Furthermore, the clinical data are consistent with those of previously published randomised trials [5, 8, 11] and enables us to maximise external validity by observing patients in a 'real life' or 'natural' setting. This approach has been recently advocated for prospective economic evaluation of new pharmaceuticals [19, 20]. This is further supported by the observation of different patterns of use of RHu-G-CSF in our observational cohort versus protocol-driven randomised trials, which have predetermined length of utilisation and average dose, not always those which would be used in normal practice.

Outpatient care resource utilisation data were not available through retrospective data collection. However, outpatient care represents a marginal share of the total cost of hospitalisation for ABMT and its cost is not likely to be affected by RHu-G-CSF. In addition, this method of data collection has the advantage of being unbiased providing that the investigators remain blind to the treatment status.

The main cost driver is length of stay in hospital. The costing methodology used to value hospital cost remains unsatisfactory for two main reasons. Estimates per day are difficult to use in specific impact of procedures such as RHu-G-CSF. Since they do not bill and generally do not use analytic accounting systems, estimates per day are the usual basis for economic analyses performed in the European context and are related to the hospital financial systems (e.g. in France). Also, like most published studies, our analysis was structured on the basic assumption of the variability of hospital costs. If this is likely to be true at the macro level over a long period of time, this may not be relevant locally and on a short-term basis.

Taking these limitations into consideration, this study supports the hypothesis that the use of RHu-G-CSF in patients undergoing ABMT is associated with a modest reduction in direct medical costs, which remain high for bone-marrow transplantation. With RHu-G-CSF, the graft is better tolerated without inducing marked side-effects. Compared to no RHu-G-CSF, the use of RHu-G-CSF improves therapeutic efficacy and quality of life patients in reducing length and severity of neutropenia, incidence of mucosity and length of stay in a sterile unit and in hospital.

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