Prevention of febrile leucopenia after chemotherapy in high-risk breast cancer patients: no significant difference between granulocyte-colony stimulating growth factor or ciprofloxacin plus amphotericin B


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 use of recombinant human granulocyte-colony stimulating growth factor (rhG-CSF) or ciprofloxacin and amphotericin B (CAB) in the prevention of febrile leucopenia (FL) after high-dose chemotherapy for metastatic breast cancer. Chemotherapy comprised cyclophosphamide, 5-fluorouracil (5-FU) plus epirubicin or methotrexate (the doses were reported). Group I received rhG-CSF 263 microg subcutaneously, once daily, on days 3 to 12. Group II received 500-mg (2 x 250 mg) oral ciprofloxacin daily, and 20-mL (4 x 5 mL) oral amphotericin B suspension (100 mg/mL) daily, both on days 3 to 17.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised female chemotherapy-naive patients aged 65 years or less, with single and multiple metastatic breast cancer, who were undergoing chemotherapy. The chemotherapy scheme consisted of three courses of intravenous (i.v.) cyclophosphamide (1,500 mg/m²), epirubicin (80 mg/m²) and 5-FU (1,500 or 1,000 mg/m²) on day 1. This was followed on day one by a further 3 courses of i.v. cyclophosphamide (1,500 mg/m²) and 5-FU (600 mg/m²). On day 2 patients received i.v. methotrexate (1,500 mg/m²). Due to an unethically high number of FL cases, the dosage of 5-FU on day one was reduced to 1,000 mg/m² for the last 18 patients included in the study.

Setting
The setting was tertiary care. The economic study was carried out in Groningen, the Netherlands.

Dates to which data relate
The dates to which the effectiveness evidence, resources and prices related, were not stated. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
It was unclear whether the costing was undertaken on the same study sample as that used in the effectiveness analysis.
Study sample
No power calculations were used to determine the sample size. Before chemotherapy, the patients were randomised to either group I (rhG-CSF) or group II (CAB). Forty patients were included in the study, 18 were randomised to group I while 22 were randomised to group II. Seven patients allocated to group II were excluded from the analysis as they switched to rhG-CSF. Three of these patients stopped treatment due to disease progression or death from the disease.

Study design
The study was a prospective randomised controlled trial that was carried out in a single centre. The method of randomisation was not reported. In addition, the authors did not report how the study sample was selected. The duration of follow-up was not stated. However, leucocyte counts were performed before the course and once between days 10 and 14 after the start of the course. Three patients died in the course of treatment.

Analysis of effectiveness
The analysis of the clinical study appears to have been conducted on the basis of treatment completers only, although this was not explicitly stated. The primary outcomes were the reduction in FL and the number of hospital days. FL was defined as a leucocyte count of less than 1.0 x10^9/L (grade IV on WHO toxicity scale) combined with fever (temperature higher than 38.5 degrees C), and was followed by hospitalisation and standard analyses of possible infectious foci. Patients were discharged when the temperature was normalised (lower than 37.5 degrees C for at least 24 hours) and when the leucocyte count was above 1.0 x10^9/L. The characteristics of the patients (age, metastases and metastatic sites) in the two groups appear to have been comparable.

Effectiveness results
Seven patients in group I (n=18) were hospitalised after 10 of the 108 courses for FL. Seven patients in group II (n=22) were hospitalised after 7 of the 98 courses, (p = non significant).

Before 5-FU dose reduction, 7 of 9 patients in group I and 6 of 13 patients in group II suffered from FL, after 54 (group I) and 49 (group II) courses, respectively, (p = non significant).

After 5-FU dose reduction for the last 18 patients studied (9 in each group), FL declined equally in both groups. There were no patients in group I suffering from FL and only one patient in group II.

The median hospital duration was 6 days (range: 5 - 9) for group I and 7 days (range: 5 - 10) for group II (p = non significant).

No infection-relation death was observed.

Twenty-two (20%) of the 108 courses received in group I were followed by grade IV leucopenia, compared with 41 (42%) of the 98 courses received in group II, (p<0.0025).

Grade IV leucopenia was followed by fever in 10 (45%) of the 22 courses received in group I, compared with 7 (17%) of the 41 courses received in group II, (p<0.025)

Clinical conclusions
The authors concluded that the results showed no significant difference in the incidence of hospitalisation due to FL between the two groups. However, in the group receiving CAB, a larger number of patients appear to have been at risk of developing fever with a significantly higher incidence of grade IV leucopenia. The authors noted that, although the reduction in the dosage of 5-FU affected the overall incidence of FL, this did not result in a significant difference in FL between the groups.

Measure of benefits used in the economic analysis
No summary measure of benefit was derived. The study was therefore classified as a cost-consequences analysis.

**Direct costs**
Discounting was carried out, which was appropriate given that the costs were incurred during one hospitalisation period. The cost boundary of the health service provider was adopted. The quantities measured comprised the number of days spent in hospital and the medications (CAB and rhG-CSF) used. It was unclear whether the quantities and costs were estimated using actual data gathered during the study or from another source. The source of the costs was a study conducted in the authors' institution, while medication costs were derived from wholesale prices. No dates were reported.

**Statistical analysis of costs**
The costs were treated in a stochastic manner. The costs were analysed using the Mann-Whitney U test, where p-values of less than or equal to 0.05 were considered significant.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analyses were undertaken.

**Estimated benefits used in the economic analysis**
No summary measure of benefit was derived. See the 'Effectiveness Results' section.

**Cost results**
No difference was found between the groups in terms of regular oncology care and additional costs. The median cost per hospitalisation was $2,774 (range: 2,410 - 3,866) in group I and $3,138 (range: 2,410 - 4,230) in group II. The p-values were not reported for the cost results.

The costs of antibiotic treatment were also comparable, median $332 (range: 40 - 734) in group I versus median $439 (range: 108 - 594) in group II.

The costs of rhG-CSF ($1,085 per course) were 6.6 times higher than CAB ($164 per course).

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors' conclusions**
There was no significant difference in the incidence of hospitalisation due to febrile leucopenia (FL) in the two groups. However, in the group receiving ciprofloxacin and amphotericin B (CAB), a larger number of patients appear to have been at risk of developing fever with a significantly higher incidence of grade IV leucopenia. The authors concluded that prophylactic CAB might be considered a reasonable alternative to recombinant human granulocyte-colony stimulating growth factor (rhG-CSF) in patients at high risk of FL. The economic aspect adds to the attraction of this alternative. The study also indicated that prophylactic CAB has similar efficacy to rhG-CSF in this setting and was
more cost-effective.

**CRD COMMENTARY - Selection of comparators**
No explicit justification was given for the choice of the comparator, but it would appear to be the standard practice in the authors’ setting. You should decide whether the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The study used a randomised controlled study design, which was appropriate for the study question. The study sample appears to have been representative of the study population, although the method used to select the sample was not reported. The authors did not report the method of randomisation, or whether blinding or concealment of treatment allocation took place. Although the internal validity of randomised controlled trials is likely, in general, to be reasonable due to the randomisation process, the lack of detail reported makes it difficult to be confident. In addition, the authors indicated that there was a reduction in the dosage of chemotherapy for the last 18 patients included in the study, which may compromise their study. However, statistical analyses were carried out that indicated there was no significant difference in FL on account of this change.

**Validity of estimate of measure of benefit**
No summary measure of benefit was used in the economic evaluation. The analysis was therefore categorised as a cost-consequences study.

**Validity of estimate of costs**
The study was conducted from the perspective of the health service provider. It appears that all the costs relevant to this perspective have been included in the analysis. Some of the costs and quantities were reported separately, but no price year was reported. The lack of detail will limit the reproducibility of the results in other settings. Statistical analyses of the quantities and costs were performed. Discounting was unnecessary since all of the costs were incurred in one year, and was not conducted.

**Other issues**
The authors compared some of their effectiveness findings with those from another study, but did not address the issue of the generalisability of their findings. The authors do not appear to have presented their findings selectively and their conclusions reflect the scope of their analysis.

**Implications of the study**
The authors highlighted the fact that, although their results indicate that CAB appears to be an effective alternative for rhG-CSF in preventing FL in high-risk patients, there is a need for future placebo-controlled studies to support this conclusion.

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None stated.

**Bibliographic details**

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