A randomized, crossover comparison of standard-dose versus low-dose lenograstim in the prophylaxis of post-chemotherapy neutropenia
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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 use of half of the standard dose of lenograstim (HSDL; 131.5 microg, equivalent to half a vial of Euprotin) after standard chemotherapy in patients with solid tumours.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult outpatients with a histologically confirmed diagnosis of solid tumour and without a history of bone marrow involvement, who were receiving chemotherapy. The patients were included if they had a prior episode of neutropenia in an earlier cycle. Patients that received chemotherapy with which the likelihood of grade III or IV neutropenia was more than 50%, or with prognostic factors suggesting a greater likelihood of serious infections (compromising bone marrow reserve, advanced disease, co-morbidity and elderly patients), were also included. Additional criteria for inclusion were: age older than 18 years; signed informed consent; performance status less than 3; adequate bone marrow reserve at entry (absolute neutrophil count, ANC, of at least 1,500 and a platelet count of at least 100,000); and life expectancy of at least 3 months.

Patients with a known history of intolerance or allergy to the growth factors and social, medical or psychiatric problems that could compromise protocol compliance were excluded.

Setting
The setting was a hospital. The economic analysis was carried out in Lleida, Spain.

Dates to which data relate
The effectiveness data were collected between May 1997 and April 1999. The resource quantities were obtained during the period of the study. No prices were given, therefore, 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
The costing was based on the resources consumed during the effectiveness study period.
**Study sample**

It was stated that a power of at least 80% was required with a significance level of 0.05, although the difference between the groups that they wanted to detect was not stated. All consecutive adult patients with a histologically confirmed diagnosis of solid tumour and without a history of bone marrow involvement, who were receiving chemotherapy, were eligible for the study. The initial study sample seems to have been appropriate according to the recommendations of the American Society of Clinical Oncology (expected incidence should be greater than 40%), in terms of the use of colony-stimulating factors to avoid neutropenia due to chemotherapy.

Forty-four patients were included in the study. Of these, 39 (88.6%) had an episode of neutropenia in the previous cycle, and 5 (11.4%) were at a greater than 50% risk of neutropenia grade III to IV and co-morbidity. The total number of courses administered with lenograstim was 120, with a mean of 3 courses per eligible patient (range: 1 - 6). Efficacy was studied for those patients who received at least two cycles of chemotherapy with lenograstim without any change in the regimen or dose of chemotherapy. A total of 120 courses were analysed for toxicity and 116 for efficacy.

**Study design**

This was a prospective, randomised crossover trial carried out in a single centre. The method of randomisation used in the first cycle was not reported. The patients were randomised to receive SDL or HSDL daily for 10 days (days 5 to 14). In the next cycle of chemotherapy, patients crossed over to the alternate dose of lenograstim. After two cycles of chemotherapy, patients received alternating SDL and HSDL in successive cycles until the myelosuppressive treatment was completed.

The duration of follow-up of the patients was according to the duration of the chemotherapy treatment and consequent administration of lenograstim. Four patients received only one course of chemotherapy, one of them owing to disease progression and three due to intolerable toxicity of their chemotherapy (2 in each treatment arm). The efficacy of lenograstim was not taken into account for these patients. As one of the inclusion criteria was the patients' signing of informed consent, the patients, doctors and investigators were aware of the planned analysis.

**Analysis of effectiveness**

The analysis of the clinical study was conducted on the basis of treatment completers only. Among the 44 eligible patients, 4 were excluded from the analysis of efficacy. The outcomes compared were efficacy and toxicity. Efficacy was considered by means of the severity of neutropenia, frequency of hospital admission, and frequency of fever. In addition, the ANC, total leukocytes, and platelet count were assessed at days +5, +8, +12 and +15. Toxicity was assessed through the reporting of secondary effects such as nausea and vomiting, bone pain, and local irritation.

**Effectiveness results**

The rate of neutropenia grade III to IV was 20% in patients with HSDL (20%) and 12% in patients with SDL, (p=0.1).

It was stated that the frequencies of fever and hospital admission were not affected by the dose of lenograstim. Three patients had fever with SDL, of which 2 were admitted to the hospital. Two patients had fever and neutropenia with HSDL, of which one was admitted to the hospital.

The mean ACN (expressed as x10^9/L) with HSDL was 5.0 at day +5, 8.6 at day +8, 5.4 at day +12 and 7.5 at day +15, compared with 5.3 (day 5), 10.7 (day 8), 8.3 (day 12) and 11.4 (day 15) with SDL, (p=0.324).

The mean values for total leukocytes (expressed as x10^9/L) with HSDL were 7.7 at day +5, 11.9 at day +8, 9.2 at day +12 and 11.3 at day +15, compared with 8.5 (day 5), 13.9 (day 8), 12.5 (day 12) and 14.8 (day 15) with SDL, (p=0.862).

It was stated that there were no statistically significant differences in platelet count, leukocytes, or ANC on the different days of the cycle, or in ANC between the first and any subsequent cycles of therapy. However, these data were not reported.

In terms of toxicity, secondary effects were more common with HSDL than with SDL, although it was not reported if
the differences were statistically significant. Nausea and vomiting was the most common side effect. This occurred in 8% of courses with HSDL and in 6% of courses with SDL. Bone pain was observed in 8% of patients with HSDL and in 3% of patients with SDL. Lenograstim was withdrawn for 2 patients receiving HSDL and for 1 with SDL, because of its toxicity.

Clinical conclusions
The differences between SDL and HSDL doses were reported not to be statistically significant. HSDL was shown to be as effective as SDL in the prevention of neutropenia after moderately myelosuppressive chemotherapy, in patients with solid tumours.

Measure of benefits used in the economic analysis
The authors reported that differences in the clinical effectiveness results for both doses, HSDL and SDL, were not statistically significant. Therefore, a cost-minimisation analysis was conducted and no summary measure of benefit was used in the economic analysis.

Direct costs
Only the resource quantities for therapeutic drug use were reported, but not the costs. The cost categories were lenograstim use, hospital admissions, outpatient visits and antibiotic use. Discounting was irrelevant since the study period was less than one year. The authors gave no cost information for the categories of hospital admission, outpatient visits or antibiotic use, stating that there was no difference between HSDL and SDL.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were not reported.

Currency
No currency was reported.

Sensitivity analysis
No sensitivity analysis was reported.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
There was stated to be a 50% reduction in the cost of lenograstim with HSDL, given that there were no differences in terms of the incidence or duration of hospital admission, antibiotic use, or outpatient visits. However, the actual cost results were not stated.

Synthesis of costs and benefits
Not applicable due to the cost-minimisation approach adopted.
Authors’ conclusions
Half of the standard dose of lenograstim (HSDL) was as effective as the standard dose (SDL) in limiting the severity of neutropenia, and in reducing the frequency of episodes of fever and hospital admission, after chemotherapy in solid tumours. Therefore, the use of HSDL was cost-effective in neutropenia prophylaxis for the chosen setting.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator was that it represented the actual and recommended practice in the chosen setting.

Validity of estimate of measure of effectiveness
The analysis used a single randomised crossover study that seems to have been appropriate for the study question. There was evidence that the study sample was representative of the study population. A crossover trial was used to eliminate any bias caused by differences in the type of chemotherapy, tumour or the patients' characteristics. Therefore, the patient groups seem to have been comparable at analysis. Although a randomised control trial was conducted, the outcomes were analysed for patients who received at least two cycles of chemotherapy with lenograstim, without any change in the regimen or dose of chemotherapy. Due to this fact, four patients were excluded from the analysis of efficacy. In addition, while it was stated that starting the lenograstim therapy on day +5 reduced costs while maintaining efficacy, no comparison was made with courses in which lenograstim was administered since the first day.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was, therefore, categorised as a cost-consequences study. The authors carried out a cost-minimisation analysis because they showed there were no statistically significant differences in the effectiveness of both doses of lenograstim. However, given the presence of uncertainty, it is impossible for the two technologies to be precisely equivalent. On average, there is also likely to be a difference, which should be valued by the difference in resource use. For example, if the savings obtained by using HSDL are very small, it might be worth paying the extra to use SDL, even if the average gain in effectiveness is also small.

Validity of estimate of costs
The only cost considered in the study was the cost of lenograstim. However, this cost was not reported since, for HSDL, it was assumed to be half of that for SDL. The costs related to the frequency and duration of hospitalisation were omitted since the authors stated that there was no difference between the two alternative doses. Only quantities were reported, not costs, therefore, no statistical analysis of the costs was performed. If the assumption about the costs is correct, this should not introduce uncertainty into the reliability of the conclusions. However, there is certainly a lack of transparency in the presentation of the results.

Other issues
The authors made appropriate comparisons of their findings with those from other studies and addressed the issue of generalisability to other settings. The authors stated that the results of this study should be applied similar settings and not to other, more intensive, chemotherapy regimens. The authors appear to have presented their results selectively. Some information was not supported by the data, such as no differences in the duration of hospital admissions. The study enrolled adult outpatients with a histologically confirmed diagnosis of solid tumour and without a previous history of bone marrow involvement, who were receiving chemotherapy, and this was reflected in the authors' conclusions. The authors did not report any limitation to their study.

Implications of the study
The authors warn about the importance of giving appropriate recommendations of the optimal dose or duration of G-CSF in order to save resources in the health system. The extended use of G-CSF, even in patients for whom the efficacy has not been proven to be conclusive, has led to a considerable increase in cost. They suggest that a randomised
study should be conducted to compare whether a shorter duration (10 days) of the therapy shows similar efficacy and lower cost. This was a reasonably well-designed study, but it lacked a report of the costs.

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