Summary
As part of an NHS Executive Trent regional initiative we considered the role and cost-effectiveness of high dose chemotherapy in the treatment of relapsed Hodgkin's disease and non-Hodgkin's lymphoma. The key trials and case series show an additional patient benefit of 0.8–1.1 life years over standard chemotherapy. We estimate incremental cost per life year gained of £12,800–£17,600, which reduces further if long-term benefits are considered. High dose chemotherapy in these conditions is both life-saving and cost-effective. © 2000 Cancer Research Campaign

Keywords: Hodgkin's disease; lymphoma; cost-effectiveness; high dose chemotherapy; transplantation

Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL) represent approximately 3–5% of all reported malignancies. Whilst the incidence of HD shows a general downwards trend, the overall incidence of NHL is gradually increasing by an estimated 3% per annum. A typical UK health authority (population 500,000) should expect to see between 60 and 70 new cases of NHL and 8–10 new cases of HD each year. Although patients with relapsed disease have historically had a very poor prognosis, new treatment strategies can now cure approximately 40–50% of suitable patients.

The use of high dose chemotherapy (HDC) initially supported by autologous bone marrow transplantation (ABMT) and, more recently, peripheral blood stem cells (PBSC), has rapidly become a routine treatment for relapsed lymphoma patients. In studies of relapsed HD patients, long-term survival rates of 50–65% have been reported using various HDC regimens (Reece et al, 1991; Bierman et al, 1993; Chopra et al, 1993; Goldstone et al, 1993). Similar results have been shown for relapsed high/intermediate grade NHL patients (Philip et al, 1991, 1995; Salzman et al, 1997). In a recent review (Beard et al, 1998) we considered the role and cost-effectiveness of HDC in the treatment of lymphoma for the Trent Institute Working Group on Acute Purchasing (TIWGAP), a regional body established to consider evidence of clinical and cost-effectiveness for new drugs and interventions. We present our pharmaco-economic findings, and draw on the key messages of these costs are unique to this unit and depend on specific case mix, whilst they are very useful for the purpose of contracting, they are not easily transferable to another unit. A more durable assessment of cost can be gained simply from drug acquisition costs and time in hospital. This can then be supplemented with specific costs applicable to that unit. The Out of Area Treatment (OATS) cost for high dose chemotherapy at this unit is.
High dose chemotherapy survival benefits and cost per LYG

| Trial Data        | Survival Benefit (mths) | LYG | Cost per LYG   |
|-------------------|-------------------------|-----|---------------|
| Hodgkin’s disease |                         |     |               |
| BNLI Trial        |                         |     |               |
| Initial trial data only | 10                      | 0.8 | £17 375       |
| 5 years extended  | 28                      | 2.3 | £6 043        |
| 10 years extended | 45                      | 3.8 | £3 658        |
| 20 years extended | 78                      | 6.5 | £2 138        |
| Long-term trial follow-up data (2 years extended) | n/a | n/a | n/a |
| Non-Hodgkin’s lymphoma |                     |     |               |
| PARMA Trial       |                         |     |               |
| Initial trial data only | 13                      | 1.1 | £12 636       |
| 5 years extended  | 27                      | 2.3 | £6 043        |
| 10 years extended | 40                      | 3.3 | £4 212        |
| 20 years extended | 66                      | 5.5 | £2 527        |
| Long-term trial follow-up data (2 years extended) | 18 | 1.5 | £9 267        |

In addition, we compared data from the larger HDC case series (Chopra et al, 1993) with outcomes of conventionally treated HD patients, as suggested by the National Cancer institute (NCI) series (Longo et al, 1992). This provided a similar magnitude of benefit for HDC, with marginal survival benefit at 11 months. A recent randomized study from the EBMT comparing standard therapy with HDC in relapsed HD which closed early due to poor accrual, showed no survival advantage for the HDC arm (Schmitz et al, 1999). However, this was because the majority of patients who relapsed after standard therapy were then salvaged with HDC. Full details are not yet available but the authors concluded that HDC is still the treatment of choice for HD in first relapse.

Marginal benefits of HDC in relapsed NHL patients

The PARMA group (Philip et al, 1995) showed an initial response rate of 84% after HD and 44% after standard salvage treatment in relapsed NHL patients. At 5 years the event-free survival was significantly greater in the HDC arm (46% vs 12%, P = 0.001) and overall survival was also superior (53% vs 32%). The marginal survival benefit was calculated as 13 months (1.1 LYG) per patient, in favour of HDC, and again a forward projection of benefits was taken beyond the original trial period (Table 1). Recently updated trial data (Philip et al, 1998), taken over an 8-year follow-up period, suggests that patient survival benefits are sustained and significant differences remain over the long-term. This provides further support to our original projection of benefits beyond the initial trial period. The 8-year event-free survival (36% vs 11%, P < 0.002) and overall survival (47% vs 27%, P < 0.042) figures correspond to an estimated marginal survival benefit of 18 months (1.5 LYG) and a cost per LYG of £9 267 (Table 1).

Sensitivity analysis

The results of the sensitivity analysis are summarized in graphical form, allowing different combinations of costs and benefits to be considered as required (Figures 1 and 2). Each graph shows three separate series, corresponding to different levels of clinical benefit and representing a level of cost-effectiveness, tracking cost per life year values against the marginal cost of HDC. If the benefits are assumed to be equal to those seen within the trial the cost-effectiveness of HDC in both NHL and HD remains under £25 000 per LYG, even when the marginal cost of HDC is increased to £20 000.
DISCUSSION

The strength of observational study evidence strongly supports the use of HDC in relapsed HD and relapsed high/intermediate grade NHL. There is little RCT evidence available and further trials are unlikely to take place due to recruitment difficulties for the standard therapy arm. The BNLI trial did not reach a statistically significant survival advantage as the trial was stopped early. The EBMT trial was essentially a study comparing early with late HDC in relapsed Hodgkin’s disease. Recently revised EBMT guidelines provide a useful framework within which to consider the role of HDC for treatment of HD and NHL (Goldman et al, 1998).

The cost-effectiveness arguments for the use of HDC in relapsed NHL and relapsed HD patients are strong, even under sensitivity analysis involving both costs and benefits. The cost-effectiveness ratios, at £12 636 and £17 375 respectively, are certainly comparable with similarly supported therapies and fall under generally accepted UK cost-effectiveness thresholds of around £20 000 per LYG (Stevens et al, 1995). Even using these conservative cost estimates, if 5-year projected benefits are included the cost per LYG figures are reduced by around 50%.

The actual marginal cost of HDC may be significantly lower than that used in our analysis as the high initial costs of HDC would be partially offset by the reduced likelihood of further chemotherapy following relapse. Patients with high grade NHL who relapse tend to have aggressive disease and do not survive very long. Patients with relapsed HD may exhibit a chronic relapsing remitting condition requiring regular treatment and supportive care, but long-term survival is unusual. Furthermore, this analysis has not taken into account difference in the quality of life between patients cured of their lymphoma and those receiving palliative therapy for incurable disease.

Cost-effectiveness analyses of new treatments are an integral part of the move towards evidence-based purchasing for all health services, including oncology. The establishment of the National Institute for Clinical Excellence (NICE) has formalized the efforts.
of TIWGAP and similar regional development and evaluation bodies currently conducting cost-effectiveness analysis for the Inter-DEC (Department of Health, 1998). Clinicians and purchasers alike need to remain aware of cost-effectiveness issues and empower themselves in such an evidence-based environment.

High dose chemotherapy in relapsed HD and NHL is both a clinically effective and cost-effective treatment strategy.

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