Clin. Lab. Haem.
2000, **22**, 61–72

REVIEW

Autologous stem cell transplantation for malignancy: a systematic review of the literature

S.J. SIMNETT* **MRC CancerTrials Office, Cambridge, UK*
L.A. STEWART* *†CRC Wessex Medical Oncology Unit, Southampton, UK*
J. SWEETENHAM† *‡University of Leeds, Leeds, UK*
G. MORGAN‡ *§ICRF Cancer Medicine Research Unit, Leeds, UK*
P.W.M. JOHNSON§

Summary A systematic review of the literature was undertaken to assess what published evidence is currently available to support the increasing use of autologous stem cell transplantation (ASCT), and to evaluate the published data with regard to the comparative cost of high-dose and conventional therapy. The review aimed to identify all published, randomized controlled trials (RCTs) comparing high-dose therapy (HDT) with ASCT versus conventional chemotherapy (CC) in acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and breast, lung, testicular and ovarian cancer. The review also aimed to identify all studies that had compared the cost of the two treatment strategies. Reports were identified by systematic searches of Cancerlit, Embase and Medline, and handsearching of several conference proceedings. Where possible, pooled odds ratios (ORs) were calculated according to the fixed-effect model. A total of 18 randomized trials were identified in acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and breast, lung and testicular cancer. Trials were generally small and no disease site had sufficient information to determine reliably whether high-dose therapy with autologous transplant is more effective than CC. Five studies were identified that compared the cost of the two treatments. These found the cost of HDT to be between one and four times higher than that of CC. Further randomized trials are required. Where appropriate, these should include economic assessment and assessments of long-term toxicity.

Keywords Autologous stem cell transplantation, high-dose therapy, conventional chemotherapy

Introduction

The use of high-dose therapy (HDT) employing myeloablative treatment and haematopoietic rescue is increasing in both haematological and non-haematological malignancies. Data from the International Bone Marrow Transplantation Registry and the Autologous Blood and Bone Marrow Transplant Registry estimated that around 500 autologous transplants were performed worldwide in 1970 (Horowitz & Rowlings 1997) with this figure rising to over 17,000 in 1995. The factors behind this increase have been widely discussed, and relate to the unsatisfactory results of conventional treatment, reports of dose–response relationships for some malignancies (at least *in vitro*), encouraging reports from single institutions and registry-based series, together with reductions in morbidity owing to the use of growth factor-mobilized haemopoietic progenitors and improvements in supportive care. These have encouraged the use of progenitor cell transplants in the treatment of a number of diseases where the risks of therapy were previously thought to outweigh the potential benefits.

Despite several thousand publications reporting the results of transplant series, there is still great uncertainty

Accepted for publication 5 October 1999
Correspondence: L.A. Stewart, MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW, UK.

as to the true effectiveness of HDT and progenitor cell transplants. The treatment is often viewed as expensive and toxic. A systematic review of the randomized literature was therefore undertaken (Johnson *et al*. 1998) to evaluate the efficacy of high-dose therapy with autologous transplantation (HDT(autol)) compared with conventional chemotherapy (CC). This review as a whole investigated both autologous and allogeneic transplantation. The latter also considered evidence from non-randomized controlled clinical trials because insufficient randomized evidence was available. This paper, however, is restricted to the evidence relating to autologous transplantation where only randomized controlled trials were considered.) Results for acute lymphoblastic leukaemia, malignant lymphoma, multiple myeloma, breast, lung and testicular cancer are presented here. No randomized trials were identified for chronic myeloid and chronic lymphocytic leukaemia or for ovarian cancer. The data on autologous transplantation in acute myeloid leukaemia are not reported because an individual patient data meta-analysis has recently been completed by the International Acute Myeloid Leukaemia Collaborative Group (M. Clarke, personal communication), which will give a more reliable assessment of effectiveness. The disease sites investigated represent the areas in which most transplant activity has been focused and where, owing to the incidence of the illnesses, the clinical and economic impact is likely to be greatest. The literature on the comparative cost of HDT and progenitor cell transplantation vs. conventional therapy has also been systematically reviewed and is included in this report.

Methods

The methods for trial identification and analysis of results were specified prospectively. Published studies were identified using electronic literature searches of Cancerlit, Embase, Medline and the NHS Economic Evaluation Database (completed on January 1, 1997). A second search for randomized controlled trials (RCTs) using a modified version of the Cochrane Collaboration optimal search strategy was completed on June 1, 1997. This was supplemented by hand searching conference proceedings of the European Bone Marrow Transplantation Group (1992–97), International Society for Experimental Hematology (1992–96) and European Haematology Association (1994–96). In addition, the UK Coordinating Committee on Cancer Research Cancer Trials Register and the National Cancer Institute PDQ database were searched for reports of eligible ongoing and unpublished trials, although no additional information was sought from these trials.

Only randomized trials were included in the analysis. Tables of non-randomized studies and of ongoing randomized trials are presented elsewhere (Johnson *et al*. 1998). Randomization could have been at any stage of the illness, for example as first-line therapy, consolidation of response or second-line therapy. Studies should also have reported on overall survival or progression-free survival, where progression-free survival was defined as patients alive and progression-free at the time of analysis. There were no language restrictions and no judgement was made as to whether the high-dose therapy was truly myeloablative. For economic comparisons, studies were included if the report made an economic evaluation of HDT compared with CC. Decisions on the inclusion of potentially eligible papers, together with data extraction, were carried out independently by two reviewers. Any discrepancies were resolved by discussion and by seeking a third opinion where necessary.

Odds ratios (ORs) were combined using the Peto method according to the fixed-effects model. Where ORs were not presented in the paper at the time-points of interest, the statistic was calculated from observed and expected number of events taken from the paper or calculated from survival curves. In-house software was used to perform statistical analysis and to produce plots. The χ^2-test for heterogeneity (Early Breast Cancer Trialists' Collaborative Group 1990) was used to test for gross statistical heterogeneity between individual trials and the χ^2-test for interaction to test for gross statistical heterogeneity between groups of trials. Unless otherwise stated, all *P*-values are on 1 degree of freedom.

Results

Across all the disease sites investigated, 18 RCTs (Humblet *et al*. 1987; Fiere *et al*. 1990; Fiere *et al*. 1994; Bernasconi *et al*. 1992; Chevreau *et al*. 1993; Linch *et al*. 1993; Attal *et al*. 1994; Sebban *et al*. 1994; Bezwoda, Seymour & Dansey 1995; Fermand *et al*. 1995; Ljungman *et al*. 1995; Philip *et al*. 1995; Verdonck *et al*. 1995; Gisselbrecht *et al*. 1996; Martelli *et al*. 1996; Peters *et al*. 1996; Gianni *et al*. 1997; Haioun *et al*. 1997; Santini *et al*. 1999) of HDT(autol) versus conventional therapy were identified, the majority of which used bone marrow as the source of progenitor cells. Three trials were in adult acute lymphoblastic leukaemia, seven in non-Hodgkin's lymphoma, one in Hodgkin's disease, two in multiple myeloma, three in breast cancer, one each in lung cancer and germ-cell tumours, and none in ovarian cancer, chronic myeloid leukaemia or chronic lymphocytic leukaemia. The results of individual trials are summarized in Table 1, and Table 2 gives a summary

Table 1. Summary of the findings of trials used in this review

			Survival			Progression-free survival				
Disease	Years of recruitment	Number of patients	HDT (autol):CC	Statistics in paper	Calculated OR (99% CI)	HDT (autol):CC	Statistics in paper	Calculated OR (99% CI)	Comments	No of ongoing trials
Paediatric acute lymphoblastic leukaemia										2
Adult acute lymphoblastic leukaemia										4
Fiere *et al.* (1990)	85–86	67	54 : 47 2.5 years	NS	0.75	–	NS	–	Crude survival is calculated from the number of reported events. Preliminary feasibility study prior to the study of Sebban *et al.* (1994)	
Sebban *et al.* (1994)/ Fiere *et al.* (1994)	86–91	117	41 : 31 5 years	$P < 0.05$ in Fiere *et al.* (1994), $P = 0.7$ in Sebban *et al.* (1994)*	(0.29–1.93) 0.68 (0.25–1.81) 5 years	–	0.6	–	Discrepancy in the quoted *P*-values for survival. Possible that the value form the abstract refers to a median survival and that from the paper is for the log rank test	
Bernasconi *et al.* (1992)	87–90	29	–	–	–	44 : 35 2 years	NS	0.68 (0.10–4.70) 2 years		
Chronic myeloid leukaemia	–									2
Chronic lymphocytic leukaemia	–									0
Non-Hodgkin's lymphoma										9 (all stages and points of therapy)
First-line therapy										
Gianni *et al.* (1997)	87–93	98	81 : 68 4 years	$P = 0.09$	0.50 (0.15–1.65) 4 years	81 : 58 4 years	$P = 0.004$	0.34 (0.11–1.04) 4 years	Crossover design, HDT (autol) given to all patients at progression after CC Interim results	
Santini *et al.* (1997)	92–95	124	67 : 65 3 years	–	0.95 (0.36–2.53) 3 years	–	–	–		
Gisselbrecht *et al.* (1996)	93–94	302	61 : 73 at median follow-up 16 months	$P = 0.01$	–	48 : 57 at median follow-up 16 months	$P = 0.02$	–	Trial has very short follow-up	
Consolidation of first complete remission										
Haioun *et al.* (1997)	87–93	541	69 : 67 5 years	$P = 0.8$ (0.57–1.47) 5 years	0.91	63 : 59 4 years	$P = 0.2$	0.84 (0.54–1.33) 4 years	Conventional dose is intense compared with more widely used regimens	

Disease	Years of recruitment	Number of patients	Survival: HDT (autol):CC	Survival: Statistics in paper	Survival: Calculated OR (99% CI)	Progression-free survival: HDT (autol):CC	Progression-free survival: Statistics in paper	Progression-free survival: Calculated OR (99% CI)	Comments	No of ongoing trials
Consolidation of first remission in slow responders										
Martelli *et al.* (1996)	88–91	49	73 : 59 4 years	NS	0.56 (0.12–2.61) 4 years	73 : 52 4 years	NS	0.42 (0.09–1.90) 2 years	Presence of mediastinal mass at diagnosis found to be a positive prognostic factor and this was not balanced in the two arms (in favour of HDT (autol) arm)	
Verdonck *et al.* (1995)	87–94	69	56 : 85 4 years	$P = 0.12$	4.17 (1.07–16.24) 4 years	43 : 53 4 years	$P = 0.43$	1.68 (0.49–5.77) 4 years		
HDT (autol) for 2nd or 3rd remission										
Philip *et al.* (1995)	87–94	109	61 : 38 4 years	$P = 0.038$	0.41 (0.15–1.11) 4 years	46 : 19 5 years	$P = 0.001$	0.29 (0.10–0.84)	22/55 patients on HDT (autol) arm received radiotherapy, only 12/54 on CC arm	
Hodgkin's disease										3
Relapsed or resistant										
Linch *et al.* (1993)	–	40	74 : 60 2 years	$P = 0.318$	0.51 (0.09–2.87) 2 years	59 : 21 2 years	$P = 0.025$	0.2 (0.04–1.02) 2 years	Mixture of relapsed/resistant patients, no indication if this was balanced between treatment groups Follow-up is short	
Multiple myeloma										2
Attal *et al.* (1994)	90–93	204	59–39 4 years	$P = 0.03$	0.45 (0.22–0.93) 4 years	28 : 16 4 years	$P = 0.01$	0.50 (0.21–1.20) 4 years	26% of HDT (autol) patients did not receive treatment, 9 CC patients crossed-over	
Fermand *et al.* (1995)	90–94	153	82 : 67 2 years	$P = 0.28$ (0.17–1.16) 2 years	0.45	77 : 47 2 years	–	0.28 (0.12–0.66)	40% of CC patients crossed-over	
Breast cancer										14 (all stages)
Advanced/metastatic										
Bezwoda *et al.* (1995)	91–93	90	44 : 3 2 years	–	0.10 (0.03–0.35) 2 years	–	–	–	Poor survival on CC arm	
Ljungman *et al.* (1995)	89–94	9	–	–	–	–	–	–	No further information given in paper, patients included in a non-randomized comparision	
Peters *et al.* (1996)	88–95	98	23 : 38*	$P = 0.04$*		11 : 4*	$P = 0.008$*		*Ambiguity as to whether these values are median survival/ progression free survival values or not and whether the *P*-values refer to the log-rank test	
Germ cell tumours										3
Chevreau *et al.* (1993)	88–91	104	60 : 80 2 years	$P = 0.08$	2.71 (0.95–7.76) 2 years	58 : 70 at median follow-up of 24 months	–	–	Total dose of cisplatin the same in both arms	
Small cell lung cancer										3
Humblet *et al.* (1987)	80–85	45	30 : 9 2 years	$P = 0.13$	0.27 (0.04–1.82) 2 years	13 : 0	$P = 0.002$	0.13 (0.01–2.72)	Survival measure from 1st day of induction, progression-free survival from time of randomization	
Ovarian Cancer	–	0								3

CC, conventional chemotherapy; HDT (autol), high-dose therapy with autologous transplantation; OR, odds ratio; RCT, randomized controlled trial.

Table 2. Summary of the findings of randomized controlled trials (RCTs) comparing high-dose therapy with autologous progenitor cell transplantation (HDT (autol)) with conventional therapy

Disease	Number of trials	Number of patients	Summary of Review findings
Adult acute lymphoblastic leukaemia	3 RCTs	213	No evidence of a difference in overall survival or progression-free survival
Chronic myeloid leukaemia	0	0	–
Chronic lymphocytic leukaemia	0	0	–
Non-Hodgkin's lymphoma			
Component of front-line chemotherapy	6 RCTs	1183	No evidence of a overall survival or progression-free survival difference. (HDT (autol)) may have been given as first-line therapy or as consolidation of a response)
HDT (autol) for 2nd or 3rd remission	1 RCT	109	Insufficient evidence to draw conclusions. (Single trial reported an overall survival and progression-free survival advantage in favour of HDT (autol).)
Hodgkin's disease			
Relapsed or resistant	1 RCT	40	Insufficient evidence to draw conclusions (Single trial reported progression free survival advantage in favour of HDT (autol) but found no evidence of an overall survival benefit)
Multiple myeloma	2 RCTs	357	No evidence of a overall survival difference, possible progression-free survival advantage in favour of HDT (autol)
Breast cancer			
Advanced/metastatic	3 RCTs	197	Insufficient information reported in trials to allow quantitative data summation or conclusions to be drawn
Germ cell tumours	1	104	Insufficient evidence to draw conclusions. (Single trial found no evidence of an overall survival benefit. No information on progression-free survival.)
Small cell lung cancer	1	45	Insufficient evidence to draw conclusions. (Single trial reported progression-free survival advantage in favour of HDT (autol) but found no evidence of an overall survival benefit)
Ovarian cancer	0	0	–

of the available information and overall results by disease site.

Acute lymphoblastic leukaemia

Three RCTs (Fiere *et al*. 1990; 1994; Sebban *et al*. 1994; Bernasconi *et al*. 1992), including 213 patients in total, were identified. All randomized adult patients in first complete remission following induction therapy to receive HDT or conventional consolidation treatment. None of the trials reported a difference in survival or progression-free survival. Owing to incomplete data reporting, no quantitative synthesis was possible.

Non-Hodgkin's lymphoma

Seven RCTs (Philip *et al*. 1995; Verdonck *et al*. 1995; Gisselbrecht *et al*. 1996; Martelli *et al*. 1996; Haioun *et al*. 1997; Gianni *et al*. 1997; Santini *et al*. 1999) were identified, including 1192 patients randomized between 1987 and 1995. All investigated HDT in the treatment of intermediate- and high-grade lymphoma, but in patients with differing characteristics or at different stages in the history of the lymphoma.

First-line induction therapy

Three trials (Gisselbrecht *et al*. 1996; Gianni *et al*. 1997; Santini *et al*. 1999) were identified that investigated the use of HDT as a component of first-line therapy, one of which (Gianni *et al*. 1997) randomized patients to immediate versus delayed HDT on relapse. The pooled OR for survival at 3/4 years for two trials showed no evidence of a difference between the two treatments (OR = 0.77; 95% CI 0.57–1.47; Figure 1). Two trials reported on progression-free survival: one (Gianni *et al*. 1997) reported a significant benefit for HDT; the other (Gisselbrecht *et al*. 1996) reported a significant benefit for CC. Insufficient

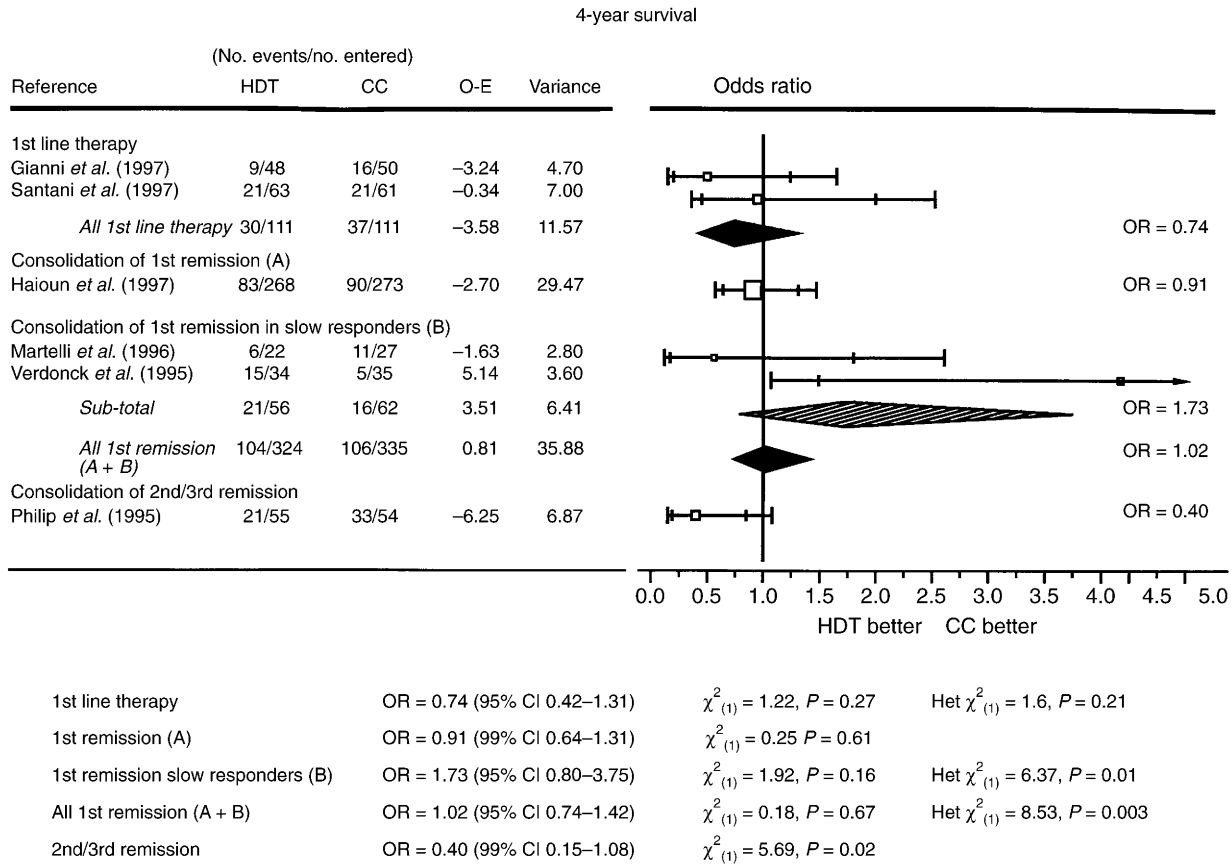


Figure 1. Randomized controlled trials comparing high-dose therapy (HDT) + autologous transplantation versus conventional chemotherapy (CC) in non-Hodgkin's lymphoma. O-E, observed-expected events.

data were included in the reports to allow summation of this data.

Consolidation of first complete remission

One comparatively large trial (Haioun *et al.* 1997) was identified. This randomized 541 patients in first complete remission who were defined as poor risk according to the Coiffier criteria (Coiffer 1991). No evidence of a difference in overall survival or progression-free survival was reported.

Consolidation of first remission in slow responders

Two RCTs (Verdonck *et al.* 1995; Martelli *et al.* 1996) were identified that included a total of 118 patients who responded slowly to first-line induction therapy. Pooled ORs for overall survival and progression-free survival at 4 years showed no evidence of a difference between treatments, with an OR of 1.73 (95% CI 0.08–3.75) for survival and an OR for progression-free survival of 0.96 (95% CI 0.47–1.99) (Figures 1 and 2, respectively).

Consolidation of first remission – all trials

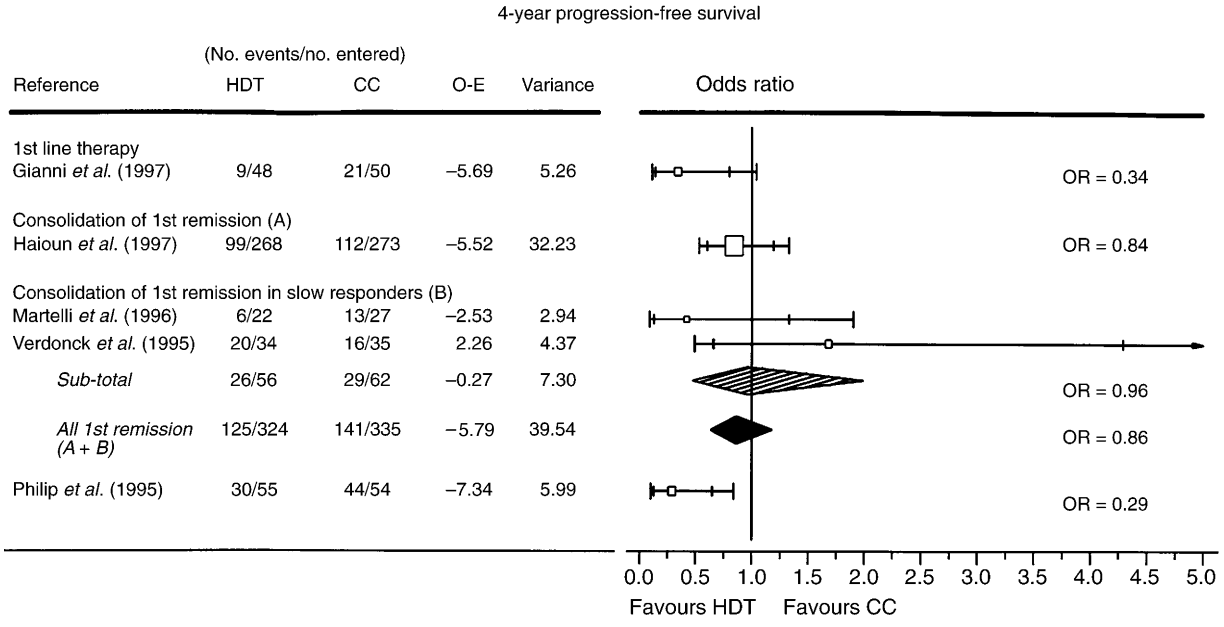
Pooling the results of 4 years' survival for all trials of consolidation of first remission gave an OR of 1.02 (95% CI 0.74–1.42) (Figure 1). For progression-free survival the overall OR was 0.86 (95% CI 0.63–1.18) (Figure 2).

Consolidation of second or third remission

One RCT (Philip *et al.* 1995) was identified that randomized 109 patients. This reported a significant overall survival and progression-free survival advantage in favour of HDT ($P = 0.038$ and $P = 0.001$, respectively; Figures 1 and 2). However, a greater number of patients (40%) on the HDT arm received radiotherapy compared with the CC arm (22%).

Hodgkin's disease

A single trial (Linch *et al.* 1993) was identified that randomized 40 patients resistant to, or relapsed following, first-line chemotherapy. The trial reported an advantage in



1st line therapy	OR = 0.34 (99% CI 0.11–1.04)	$\chi^2_{(1)} = 6.15$, $P = 0.01$	
1st remission (A)	OR = 0.84 (99% CI 0.53–1.33)	$\chi^2_{(1)} = 0.95$, $P = 0.33$	
1st remission slow responders (B)	OR = 0.96 (95% CI 0.47–1.99)	$\chi^2_{(1)} = 0.32$, $P = 0.58$	Het $\chi^2_{(1)} = 3.34$, $P = 0.07$
All 1st remission (A + B)	OR = 0.86 (95% CI 0.63–1.18)	$\chi^2_{(1)} = 0.84$, $P = 0.36$	Het $\chi^2_{(1)} = 3.45$, $P = 0.18$
2nd/3rd remission	OR = 0.29 (99% CI 0.10–0.84)	$\chi^2_{(1)} = 8.99$, $P = 0.003$	

Figure 2. Randomized controlled trials comparing high-dose therapy (HDT) + autologous transplantation versus conventional chemotherapy (CC) in non-Hodgkin's lymphoma. O-E, observed-expected events.

favour of HDT for progression-free survival ($P = 0.025$), but found no evidence of a difference in survival.

Multiple myeloma

The two trials identified (Attal *et al.* 1994; Fermand *et al.* 1995) reported on a total of 357 patients randomized between 1990 and 1994. The pooled OR of 0.68 for 2 years' survival showed no clear evidence of a difference between treatments (95% CI 0.42–1.10; $P = 0.12$; Figure 3), whilst the pooled OR of 0.39 for progression-free survival at 2 years was significantly in favour of HDT (95% CI 0.25–0.59; $P < 0.001$; Figure 4).

Solid tumours

Breast cancer. Three trials (Bezwoda *et al.* 1995; Ljungman *et al.* 1995; Peters *et al.* 1996) were identified that reported on 197 patients with advanced breast cancer randomized between 1988 and 1995. Two trials (Ljungman *et al.* 1995; Peters *et al.* 1996) randomized patients responding to initial chemotherapy, whereas in the third (Ljungman *et al.* 1995) no chemotherapy was administered prior to randomization. The largest trial (Peters *et al.* 1996), which randomized patients to immediate versus HDT(autol) on relapse, reported a significant survival benefit in favour of CC, but a significant progression-free survival benefit in favour of HDT; no details were given as to the number of patients in the conventional arm who relapsed and received a late transplant. A second trial (Ljungman *et al.* 1995) reported no survival statistics and no progression-free survival data. However, a calculated OR for survival at 2 years was conventionally significant in favour of HDT with an OR of 0.10 (99% CI 0.03–0.35; $P < 0.001$). The use of maintenance tamoxifen could potentially confound these results as a greater number of HDT patients responded to treatment and were therefore offered tamoxifen. The third trial (Peters *et al.* 1996), which randomized only nine patients, stopped early owing to poor accrual, and reported no survival or progression-free survival data. Insufficient information was included in the reports to allow data summation.

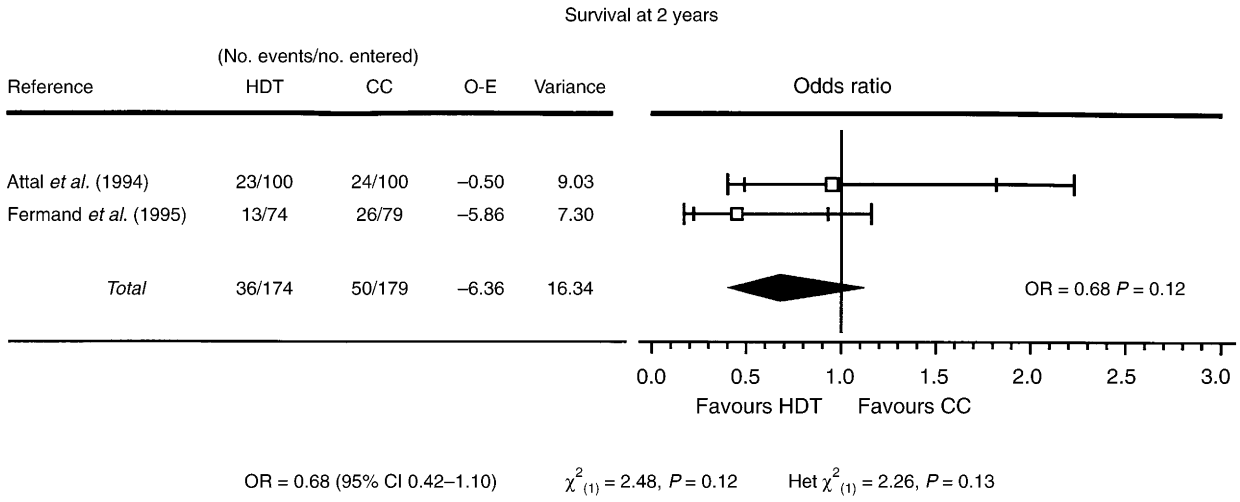


Figure 3. Randomized controlled trials comparing high-dose therapy (HDT) + autologous transplantation versus conventional chemotherapy (CC) in multiple myeloma. O-E, observed-expected events.

Testicular cancer. The single RCT (Chevreau *et al.* 1993) identified randomized 114 patients with poor prognosis metastatic germ cell tumours between 1988 and 1991. The trial found no evidence of an overall survival or progression-free survival difference between the two treatments, although the planned dose of cisplatin, the most active agent administered, was identical in both arms of the trial.

Small cell lung cancer. One trial (Humblet *et al.* 1987) was identified that randomized 45 patients in complete remission or partial remission after induction chemotherapy. The trial found no evidence of a difference in overall survival but reported a progression-free survival advantage in favour of HDT ($P = 0.002$).

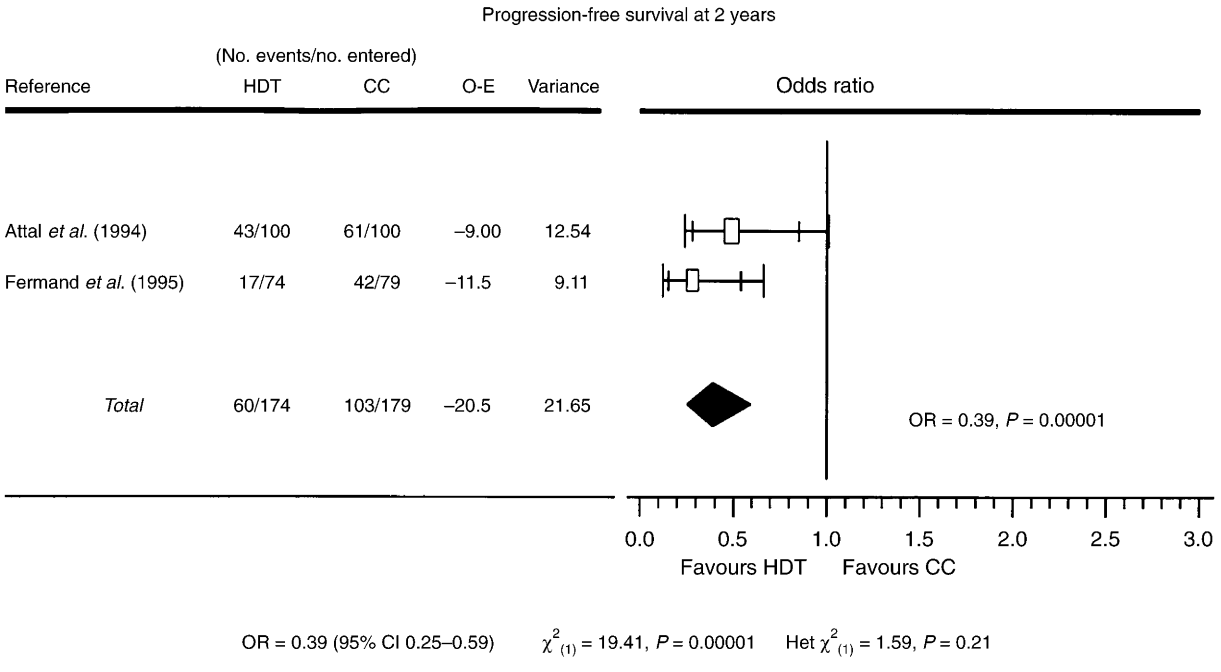


Figure 4. Randomized controlled trials comparing high-dose therapy (HDT) + autologous transplantation versus conventional chemotherapy (CC) in multiple myeloma. O-E, observed-expected events.

Economic studies

Only one study (Uyl de Groot *et al.* 1995) that based its results on the findings of an RCT was identified (Table 3). This study evaluated the cost of treating 42 of 69 patients with non-Hodgkin's lymphoma who were randomized in a trial of postremission therapy for slow responders (Verdonck *et al.* 1995) (Table 1). Twenty-one patients were treated with HDT and 21 patients with CC. No mention was made as to how the 42 patients were selected from the total number randomized. This study concluded that the average cost over the first 2 years of therapy (with discounting at 5%) was US $49,983 for HDT and US $15,285 for CC. This difference in cost was mainly a result of the additional costs incurred during the treatment period.

Four non-randomized comparisons were also identified (Desch *et al.* 1992; Hillner, Smith & Desch 1992; Henon *et al.* 1994; Zaidi, Clarke & Hutchinson 1996) (Table 3), evaluating the cost in multiple myeloma, non-Hodgkin's lymphoma, relapsed Hodgkin's disease and breast cancer. These studies found the cost of HDT to be between one and four times higher than the cost of CC.

Discussion

HDT with autologous stem cell transplantation has been under investigation for over 30 years and, for some diseases, has become established as a routine component of treatment. Despite the publication of hundreds of case series and cohort studies involving thousands of patients, few randomized trials have compared this approach with standard therapy. Consequently, the use of such treatment in many malignancies is guided by little reliable evidence and, in most cases, it is unclear whether it offers any survival advantage over conventional therapy. This systematic review was therefore undertaken to appraise the available published evidence concerning the efficacy of HDT(autol), in a number of key cancers. Although the review only includes studies reported prior to January 1997, randomized trials published since that time have supported the results of preliminary analysis and do not affect the overall conclusions of this review (Santini, Salvagno & Leoni 1998; Rodenhuis *et al.* 1998).

As this systematic review is based only on published trial reports, it could be subject to a number of potential biases (Stewart & Parmar 1993), including those relating to unavailable trials, incomplete data and restrictions on the type of analyses that could be performed. Importantly, there are a number of closed, but as yet unpublished, trials that were not available for inclusion in the review such that publication bias (Dickersin, Min & Meinert 1992) (where the results of positive trials are more likely to be published than those with 'negative' or inconclusive results) could be a problem.

For no disease site was there sufficient randomized evidence to determine reliably whether or not HDT(autol) gives superior overall or progression-free survival compared with CC. For several disease sites only single RCTs were identified. These were all small, randomizing between 45 and 109 patients, and were therefore unable to detect reliably moderate differences in survival and progression-free survival. Even for those sites where several trials were identified, the total number of patients randomized across all trials was still modest. For example, in the consolidation of slow responders in non-Hodgkin's lymphoma, two trials were identified that together included only 118 patients. Owing to the small number of published RCTs and to insufficient reporting of data in trial publications, quantitative synthesis was only possible in a few instances and the results of these analyses must be viewed with caution.

As would be expected from their small size, the results for overall survival in individual trials are mostly inconclusive, although three out of 14 trials that presented such data reported marginally significant results (at conventional levels) in favour of HDT. Of the 13 trials that reported on progression-free survival, eight found significant benefit in favour of HDT. Several of the trials were designed to compare immediate transplantation versus later transplantation and it is important to consider that in other trials patients may also have crossed-over from conventional to HDT. This could reduce the likelihood of overall survival differences despite improvements in progression-free survival, and as most reports do not specify what proportion of patients crossed-over in this way, it is difficult to determine any effect of this strategy. It must, however, be noted that patients crossing-over from conventional treatment to HDT and progenitor cell transplantation reflects current clinical practice. Evaluation of issues such as quality of life, long-term toxicity and health economics will be necessary to determine whether transplanting early or on relapse is the most appropriate strategy, if no survival difference is seen.

Data synthesis was possible only in two disease sites. For non-Hodgkin's lymphoma the overall ORs for 4-year survival are inconclusive with the results for first-line therapy favouring HDT and those for the consolidation of first remission favouring CC. On the end-point of progression-free survival, a combined OR could only be calculated for first remission; again this was inconclusive but favoured HDT. In multiple myeloma the combined OR for 2-year survival favours HDT, but is inconclusive, and for

Table 3. Summary of the economic findings in the review

Trial code	Entry years	Type of transplant	Type of evaluation	Costs included	Method for determining total resources used	Number of patients	Cost (date of cost assessment and currency if available)	Cost converted to 1993 US$	Details of sensitivity analysis	Comments
Non-Hodgkin's lymphoma										
Uyl-de Groot *et al.* (1995) Full paper	87–93	Autologous	Cost-effectiveness analysis	**	RCT/retrospective	42	(1992) HDT (autol): $49,983 CC: $15,285	HDT (autol): $51,479 CC: $15,742	Markov model predictions HDT (autol): $11,132/LYS $13,016/QALY CC: $3032/LYS $3530/QALY	HDT (autol) is more expensive and did not improve survival Dutch study Costs and QALYs discounted at 5% Costs from a randomized trial taken for the first 2 years, then costs calculated from a Markov model
Zaidi *et al.* (1996) Abstract	–	Autologous	Cost-effectiveness analysis	*	–	11	HDT (autol): $27,000 (fl18,000) CC: $6000 (fl4000)	HDT (autol): $25,473 CC: $5660		Little information supplied UK study
Myeloma – first-line therapy										
Henon *et al.* (1995) Full paper	86–91	Autologous	Cost utility analysis	**	Retrospective Cox Model	22	(1993) HDT (autol): $56,700 CC: $46,555	HDT (autol): $56,700 CC: $46,555	–	Patients were treated in France Difference in cost largely attributable to intensive treatment unit
Hodgkin's disease – treatment of recurrent disease										
Desch *et al.* (1992) Full paper	80–91	Autologous	Cost -effectiveness analysis	**	Retrospective Model	–	HDT (autol): $76,500* CC $16,300	HDT (autol): $84,577 CC: $18,021		Analysis modelled transplant usage in various disease status following recurrence *cost for what was considered to be the optimum transplant strategy (transplant in 2nd relapse). Other costs ranged from $74,000–110,100
Metastatic breast cancer										
Hillner *et al.* (1992) Full paper	90–91	Autologous	Cost-effectiveness analysis	**	Markov model	–	(1990) HDT (autol): $89,700 CC $36,100	HDT (autol): $99,171 CC: $39,911		5% discounting of costs & benefits 30-year survival tail reduced costs by 75% Clinical outcome measures were derived from the literature

*Procedure costs only; **Procedure + subsequent therapy.

CC, conventional chemotherapy; HDT (autol), high-dose therapy with autologous transplantation; LYS, Life year saved; QALY, Quality adjusted life years; RCT, randomized controlled trial.

2-year progression-free survival a conventionally significant result in favour of HDT is observed.

As discussed in the methods section, there are considerable limitations on the type of analysis possible with a systematic review of the literature such as this. In particular, not all trials present sufficient information to be included in the analyses, and the time-points for which these analyses are carried out are constrained by the data that is presented in trial reports. Consequently, all the quantitative analyses presented must be interpreted with caution. As a whole, the review has found no conclusive evidence that HDT(autol) is superior to conventional treatment in terms of survival or progression-free survival. Conversely, it has not demonstrated that it is inferior and, given the overall pattern of results, it appears to be a therapy worthy of further exploration.

Only one small economic study that used the results of an RCT as an efficacy measure was identified and it is not possible to draw conclusions as to the relative cost of HDT(autol) with CC in any disease site. It is, however, apparent from non-randomized studies that the relative costs vary widely between studies and disease sites. It is probable that this relates as much to the methodology and assumptions used in calculating the costs as to real differences, but until standard analyses are available for comparison, health economic assessment may be necessary for all the various disease sites.

There is continuing pressure from patients and physicians to broaden the application of HDT and progenitor cell transplants. At present, despite thousands of patients having been treated, there is very little reliable evidence of its efficacy. In some malignancies, for instance relapsed Hodgkin's disease or aggressive non-Hodgkin's lymphoma in second remission, the use of HDT has become so well established (on the basis of results from non-randomized studies, or very small randomized trials), that there is now no realistic prospect of conducting new trials against conventional therapy. However, for other cancers where the use of HDT/progenitor transplantation is relatively new, there is an urgent need for high-quality research to ensure that any future introduction and use is guided by reliable evidence. There are at present several ongoing randomized trials in the disease sites investigated. It is critical to ensure that a sufficiently high number of patients are randomized in these studies, and any new studies, to give sufficient power to detect moderate differences in outcome. Where appropriate, these trials should also incorporate extended follow-up in order to evaluate possible long-term toxic effects and economic evaluations, both of which are currently lacking. More complete reporting of trial results (ideally using the CONSORT (Consolidated Standards of Reporting Trials) guidelines; Begg *et al.* 1996) is also necessary so that clinical judgements can be made on all the available results of a trial, not just the highlights. It is worrying that patients are routinely treated with a therapy whose efficacy and long-term side-effects have yet to be reliably evaluated. The ideal practice should therefore be to consider entering all patients for whom autologous transplantation is a treatment option into a randomized controlled trial.

Acknowledgements

This work was funded by the UK National Health Service Technology Assessment Programme and commissioned by the NHS Centre for Reviews and Dissemination, University of York. The views expressed do not necessarily reflect those of the NHS Executive. This work was carried out by the MRC Cancer Division, Clinical Trials Unit, 5 Shaftesbury Road, Cambridge, UK. We are most grateful to Sarah Burdett for the production of the OR plots, to Maria Grosse for conducting the PDQ searches and drafting the tables of ongoing trials, to Jayne Tierney for commenting on the tables and to Mahesh Parmar for commenting on the draft report. We would like to thank Mike Clarke for assistance in identifying trials and for helpful discussions on the leukaemia overview. Thanks also to Gino Santini for providing additional information on his abstract. The assistance given by the hand searchers, Claire Johnston, Pat Cook, Rob Sambrook and Julia Bland, was greatly appreciated, as was the help given by Rupert Jakes in searching for relevant trial titles. Andy Bond's help in searching the NHS Economic Evaluation Database was also very welcome. Luc Bijnens, Giovanni Rosti and N Schmitz provided invaluable help in identifying ongoing trials. We would also like to thank the members of the Peer Review Panel: R. Leonard, A. Goldstone, R. Pinkerton, J. Sainsbury, M. Clarke and A. Horwich for their helpful discussions and comments, together with Trevor Sheldon for his help and advice throughout the planning, research and completion of this systematic review.

References

Attal M., Harousseau J.L., Stoppa A.M. *et al.* (1994) High dose therapy in multiple myeloma: a prospective randomized study of the 'Intergroup Francais du Myelome' (IFM). *Blood* **84,** 386a.

Begg C., Cho M., Eastwood S. *et al.* (1996) Improving the quality of reporting of randomized controlled trials. The CONSORT Statement. *Journal of the American Medical Association* **276,** 637–639.

Bernasconi C., Lazzarino M., Morra E. *et al.* (1992) Early intensification followed by ALLO-BMT or AUTO-BMT or a second intensifi-

cation in adult acute lymphoblastic leukaemia: a randomized multicenter study. *Leukemia* **6,** 204–208.

Bezwoda W.R., Seymour L. & Dansey R.D. (1995) High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. *Journal of Clinical Oncology* **13,** 2483–2489.

Coiffier B. (1991) Prognostic factors in Hodgkin's and non-Hodgkin's lymphomas. *Current Opinion in Oncology* **3,** 843–851.

Chevreau C., Droz J.P., Pico J.L. *et al.* (1993) Early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non-seminomatous germ cell tumours. Preliminary results of a French randomized trial. *European Urology* **23,** 213–217.

Desch C.E., Lasala M.R., Smith T.J. & Hillner B.E. (1992) The optimal timing of autologous bone marrow transplantation in Hodgkin's disease patients after a chemotherapy relapse. *Journal of Clinical Oncology* **10,** 200–209.

Dickersin K., Min Y.-I. & Meinert C.L. (1992) Factors influencing publication of research results. *Journal of the American Medical Association* **267,** 374–378.

Early Breast Cancer Trialists' Collaborative Group (1990) *Treatment of Early Breast Cancer, Vol 1. Worldwide Evidence (1985–90).* Oxford: Oxford University Press.

Fermand J.P., Ravaud P., Chevret S. *et al.* (1995) High-dose therapy and autologous blood stem cell transplantation in multiple myeloma: preliminary results of a randomized trial involving 167 patients. *Stem Cells* **13,** 156–159.

Fiere D., Broustet A., Leblond V. *et al.* (1990) Comparison of chemotherapy and autologous and allogeneic transplantation as postinduction regimen in adult acute lymphoblastic leukemia: a preliminary multicentric study. *Hamatological Bluttransfusion* **33,** 409–412.

Fiere D., Sebban C., Vernant J.P. *et al.* (1994) Long term results of chemotherapy, allogeneic or autologous bone marrow transplantation (BMT) as post remission therapy in adult acute lymphoblastic leukemia (ALL) for patients included in a prospective multicentric trial (LALA 87). *Blood* **84,** 251a.

Gianni A.M., Bregni M., Siena S. *et al.* (1997) High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *New England Journal of Medicine* **336,** 1290–1297.

Gisselbrecht C., Lepage E., Morel P. *et al.* (1996) Short and intensified treatment with autologous stem cell transplantation (ASCT) versus ACVB revimen in poor prognosis aggressive lymphoma LNH93–3 protocol. *Bone Marrow Transplantation* **19,** S153.

Haioun C., Lepage E., Gisselbrecht C. *et al.* (1997) Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87 2. *Journal of Clinical Oncology* **15,** 1131–1137.

Henon P., Donatini B., Eisenmann J.C., Becker M. & Beck Wirth G. (1995) Comparative survival, quality of life and cost-effectiveness of intensive therapy with autologous blood cell transplantation or conventional chemotherapy in multiple myeloma. *Bone marrow transplantation* **16,** 19–25.

Hillner B.E., Smith T.J. & Desch C.E. (1992) Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. *Journal of the American Medical Association* **267,** 2055–2061.

Horowitz M.M. & Rowlings P.A. (1997) An update from the International Bone Marrow Transplant Registry and the *Current Opinion in Hematology* **4,** 395–400.

Humblet Y., Symann M., Bosly A. *et al.* (1987) Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: a randomized study. *Journal of Clinical Oncology* **5,** 1864–1873.

Johnson P.W.M., Simnett S.J., Sweetenham J.W., Morgan G.J. & Stewart L.A. (1998) Bone marrow and peripheral blood stem cell transplantation for malignancy. *Health Technological Assessment* **2,** 1–188.

Linch D.C., Winfield D., Goldstone A.H. *et al.* (1993) Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* **341,** 1051–1054.

Ljungman P., Bjorkstrand B., Gahrton G. *et al.* (1995) High-dose chemotherapy in breast cancer. Promising results in combination with stem cell support. *Lakartidningen* **92,** 851–853.

Martelli M., Vignetti M., Zinzani P.L. *et al.* (1996) High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomized Italian multicenter study. *Journal of Clinical Oncology* **14,** 534–542.

Peters W.P., Jones R.B., Vredenburgh J. *et al.* (1996) A large, prospective, randomized trial of high-dose combination alkylating agents (CPB) with autologous cellular support (ABMS) as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin-based induction therapy (AFM). *Proceedings of the Annual Meeting of the American Society of Clinical Oncology* **15,** A149.

Philip T., Guglielmi C., Hagenbeek A. *et al.* (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *New England Journal of Medicine* **333,** 1540–1545.

Rodenhuis S., Richel D., van der Wall E. *et al.* (1998) Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. *The Lancet* **352,** 515–521.

Santini G., Salvagno L., Leoni P. *et al.* (1998) VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. *Journal of Clinical Oncology* **16,** 2796–2802.

Santini G., Salvagno L., Leoni P. *et al.* (2000) VACOP-B vs VACOP-B + autolgous BM transplantation (ABMT) for aggressive non-Hodgin's lymphoma. A study of the non-Hodgkin's lymphoma cooperative study group (NHLSCG). *Bone marrow Transplantation* (in press).

Sebban C., Lepage E., Vernant J.P. *et al.* (1994) Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *Journal of Clinical Oncology* **12,** 2580–2587.

Stewart L.A. & Parmar M.K.B. (1993) Meta-analysis of the literature or of individual patient data: is there a difference? *The Lancet* **341,** 418–422.

Uyl de Groot C.A., Hagenbeek A., Verdonck L.F., Lowenberg B. & Rutten F.F. (1995) Cost-effectiveness of ABMT in comparison with CHOP chemotherapy in patients with intermediate- and high-grade malignant non-Hodgkin's lymphoma (NHL). *Bone Marrow Transplantation* **16,** 463–470.

Verdonck L.F., van Putten W.L., Hagenbeek A. *et al.* (1995) Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *New England Journal of Medicine* **332,** 1045–1051.

Zaidi Y., Clarke C. & Hutchinson R. (1996) CHOP/ABMT is less cost effective than CHOP alone in intermediate and high grade malignant non-Hodgkin's lymphoma. *Bone Marrow Transplantation* **17,** 46.