Anti-Cancer Drugs 1995, **6**, Suppl 5, pp. 7–15

The importance of dose and schedule in cancer chemotherapy: haematological cancer

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Haematological cancers have been the prototype malignant diseases in which dose-intensive strategies have been tested. To date, dose intensification within the conventional dose range has not been shown to result in improved long-term survival in prospective studies. The use of haemopoietic growth factors is important in maintaining adequate doses of chemotherapy, and reducing life-threatening complications, but growth-factor supported dose intensification has yet to be shown to improve outcome in randomised clinical trials. Dose escalation with high-dose therapy and stem cell support has produced encouraging results in several haematological malignancies. Preliminary evidence is also suggesting that it may improve long-term disease-free survival for some patients, but the results of ongoing clinical trials are needed to confirm these encouraging early results.

Introduction

There is accumulating evidence that the application of dose-intensive strategies in the chemotherapy of various haematological malignancies results in improved response and survival rates. Although most of these data have been derived from single-institution phase II studies, there are a number of recently reported and ongoing clinical trials specifically designed to address the effect of dose-intensive chemotherapy on outcome compared with conventional chemotherapy, and to investigate the role of adherence to schedule. These studies have been possible largely because of the advent of recombinant haemopoietic growth factors for clinical use, and the safer and more widespread application of high-dose therapy with autologous bone marrow or peripheral blood progenitor cell transplantation (PBPCT) in haematological malignancy.

Conflicting data have emerged regarding the importance of dose intensification and scheduling. This evidence is reviewed, with particular emphasis on patients with intermediate and high-grade non-Hodgkin's lymphoma (NHL), Hodgkin's disease and acute leukaemia.

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Intensification of 'conventional-dose' chemotherapy

Non-Hodgkin's lymphoma

According to the concept of dose intensity as originally defined by Hryniuk,[1] intensification can be achieved either by increasing the doses of chemotherapy delivered in 'standard' regimens, or by increasing the number of drugs given over a unit time. The second approach also carries the theoretical advantage of reducing the likelihood of acquired drug resistance.

The development of novel regimens incorporating multiple drugs has been extensively investigated in the management of intermediate and high-grade NHL in recent years. 'Standard' combination chemotherapy for this disease with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) produces complete remission (CR) rates of 50% to 60%, with long-term disease-free survival (DFS) in 35% to 50%.[2,3] The regimen is characterised by moderately high doses of chemotherapy given at 21-day intervals, allowing recovery from the leukocyte nadir between each cycle. 'Second-generation' regimens were developed, in which myelosuppressive drugs were given, with additional non-myelosuppressive drugs added at the time of the expected leukocyte nadir. The m-BACOD (methotrexate, bleo-

mycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone)[4] regimen is a typical example. 'Third-generation' regimens were a further extension of this concept, with myelosuppressive and non-myelosuppressive drugs given on alternating weeks, completing treatment in a relatively short time, thus achieving high drug delivery per unit time. MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin)[5,6] is a typical example of this type of regimen. Phase II clinical trials of second- and third-generation regimens for NHL produced impressive response and survival figures. The initial study of the MACOP-B regimen from Vancouver reported a response rate of 100%, with a 5-year actuarial overall survival (OS) of 75%.[5]

These favourable results were not widely reproducible. Several subsequent studies of MACOP-B from other centres produced much lower response and survival figures.[7–9] In our own centre,[10] a 12-week alternating third-generation regimen (Figure 1) produced a response rate of only 57% with a 3-year actuarial OS of 47%, despite achieving a higher projected and received dose intensity than MACOP-B, calculated according to the hypothetical nine-drug regimen described by de Vita.[11]

The randomised study conducted by the South West Oncology Group in the USA provides strong evidence that the use of such dose-intensive regimens is *not* associated with improved outcome.[12] In this study, 899 patients with intermediate-grade NHL were randomised to receive either CHOP chemotherapy, or one of three dose-intensive regimens: m-BACOD, MACOP-B or ProMACE/Cyta-BOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytosine arabinoside, bleomycin, vincristine). At 3 years there was no difference in OS according to treatment group (Figure 2), and no subgroup of patients in whom dose-intensive therapy could be shown to be more effective. Furthermore, there was a trend for a higher toxic death rate in the more intensive protocols, although this did not achieve statistical significance.

Dose escalation of 'standard' chemotherapy protocols for NHL has been the subject of relatively few randomised clinical trials. In a prospective study from Canada, 238 patients were randomised between BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone) with 'standard' dose doxorubicin (25 mg/m^2, days 1 and 8) or 'escalated' dose doxorubicin (to 40 mg/m^2, days 1 and 8 from cycle 2 onwards).[13] Patients assigned to the escalated regimen received a significantly higher dose intensity of doxorubicin compared with the

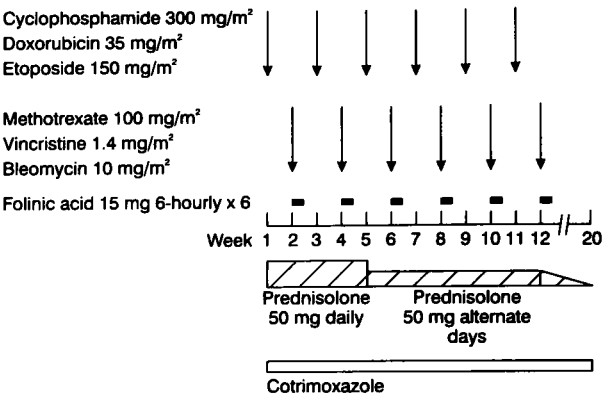

Figure 1. Schematic representation of intensive combination chemotherapy regimen for treatment of NHL. Reproduced with permission from Sweetenham JW, Mead GM, Whitehouse JMA. Intensive weekly combination chemotherapy for patients with intermediate and high grade non-Hodgkin's lymphoma. *J Clin Oncol* 1991; **9**: 2202–2209.

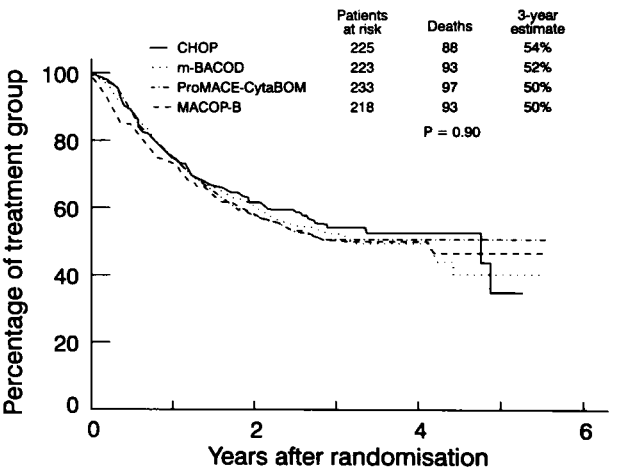

Figure 2. Overall survival for patients with advanced intermediate grade NHL according to treatment arm. Reproduced with permission from Fisher RI, Gaynor ER, Dahlberg S, *et al.* Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *New Engl J Med* 1993; **328**: 1002–1006. © 1993 The Massachusetts Medical Society.

standard-dose patients, but no difference was observed between the two groups in response rates, DFS or OS. More toxicity was observed in the escalated arm, particularly leukopenia.

Acute myeloid leukaemia

As with NHL, numerous single-institution phase II studies of dose-intensive protocols in acute myeloid leukaemia (AML) have produced superior response

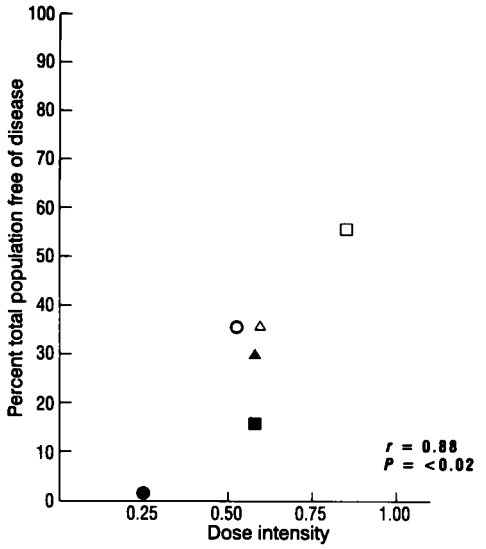

Figure 3. Relationship between the actual dose intensity of MOPP chemotherapy and DFS in Hodgkin's disease in six studies. Reproduced with permission from DeVita VT, Hubbard SM, Longo DL. The chemotherapy of lymphomas: looking back, moving forward. The Richard and Hilda Rosenthal Foundation Award Lecture. *Cancer Res* 1987; **47**: 5810–5824.

and survival rates compared with standard regimens. Dose intensification has been achieved by increasing the doses in standard regimens, or by early exposure of the leukaemia to multiple drugs.

Prospective studies have largely failed to confirm the data from intial phase II studies. Schiller *et al.* have reported results from a randomised trial in which patients received daunorubicin 60 mg/m^2 on days 1, 2 and 3, with either 1400 mg/m^2 or 6000 mg/m^2 Ara-C.[14] Overall response rates were 71% and 74% respectively, with 4-year actuarial OS of 20% and 29% ($p = 0.9$). Much higher doses of Ara-C were given in a South West Oncology Group study in which all patients received daunorubicin 45 mg/m^2 days 1, 2 and 3, and randomisation was between a total Ara-C dose of 1400 mg/m^2 or 24,000 mg/m^2.[15] No difference in response rates was observed, but early toxic deaths and neurological complications were significantly more frequent in the higher-dose arm.

In contrast, evidence from one randomised study supports the presence of a dose–response relationship for consolidation therapy of AML. In a Cancer and Leukaemia Group B (CALGB) study, 596 patients in first remission after standard induction therapy were randomised to consolidation therapy with three doses of Ara-C, receiving total doses of 500, 2000 and 18,000 mg/m^2.[16] Both DFS and OS were superior in the highest-dose group (39% and 46% respectively), compared with the lowest-dose group (21% and 31% respectively).

Dose and schedule adherence and the role of haemopoietic growth factors with conventional-dose chemotherapy

Hodgkin's disease

A retrospective analysis from Stanford University was one of the earliest to demonstrate a correlation between dose, dose rate and outcome in Hodgkin's disease.[17] Mean total dose and dose rate of mustine, procarbazine and vincristine was related to remission rate in patients receiving MOPP (mustine, vincristine, procarbazine, prednisone) chemotherapy. In particular, patients receiving less than 65% of the total planned dose of mustine had a significantly poorer survival than those who received more than 65%.

DeVita *et al.* have compared received dose intensity of MOPP chemotherapy as reported from a number of clinical trials in advanced Hodgkin's disease, demonstrating a strong correlation between actual dose intensity and DFS [11] (Figure 3). Similar results were shown for variants of MOPP including ChlVPP (chlorambucil, vinblastine, procarbazine, prednisone) and MVPP (mustine, vinblastine, procarbazine, prednisone).

Non-Hodgkin's lymphoma

The prognostic significance of received dose intensity was examined in patients receiving the LNH-87 protocol for aggressive NHL.[18] Of 311 patients included in this study, 87 had a received dose intensity below 70% of the projected intensity, calculated according to the method of Hryniuk. A lower response rate (65% vs 79%) and lower 2-year OS (61% vs 72%) was observed in patients receiving less than 70% of the projected dose intensity. This factor was independently predictive of survival in multivariate analysis.

Similar results were reported from Stanford University, in a retrospective analysis of received dose intensity in patients with aggressive NHL receiving CHOP, M-BACOD and MACOP-B.[19] Actual received dose intensity of doxorubicin greater than 70% was the single most powerful favourable prognostic factor for OS.

Retrospective analyses of dose intensity such as those summarised above must be interpreted cautiously. The dose-limiting toxicity of most combina-

tion chemotherapy regimens used for haematological cancers is myelosuppression. This is the cause of most dose reductions and delays. Factors which predispose to myelosuppression, such as performance status, presence of bone marrow infiltration, and advanced age, are also known to be powerful prognostic factors for response and survival in these diseases. Thus, the poorer outcome in patients receiving less dose-intensive chemotherapy may well be due to factors other than the chemotherapy itself.

The problem of dose-limiting myelosuppression has been overcome to some extent in recent years by the advent of recombinant haemopoietic growth factors for clinical use. The reduction in the incidence and duration of chemotherapy-induced leukopenia and of febrile neutropenia with these agents is now well documented in several tumour types.[20–22] In addition, prospective studies have demonstrated that the use of haemopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin 3 (IL-3) allow closer adherence of combination chemotherapy to dose and schedule because of the reduced severity of leukopenia. Prospective studies have therefore been designed to assess the impact of this improved dose/schedule adherence on response and survival rates.

Gerhartz *et al.* have reported results of a randomised, placebo-controlled clinical trial of recombinant human GM-CSF in patients receiving modified COP-BLAM (cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine) chemotherapy for intermediate/high-grade NHL.[23] A total of 182 patients were entered onto the study, of whom 125 received 70% or more of the planned study medication. In this population, significant reductions in the duration of leukopenia and hospitalisation were observed in GM-CSF vs placebo treated patients. In GM-CSF treated patients, 54% of the evaluable group completed treatment as scheduled, compared with 34% of placebo patients. This difference was not statistically significant. Received dose intensity calculated according to the Hryniuk method was 0.84 for treated vs 0.81 for control patients.

Despite the improvement in dose adherence, there was little effect on outcome. Response rates were slightly higher in patients receiving GM-CSF (72% vs 62% for controls), but no survival difference was observed after one year (Figure 4).

In addition, the exclusion from analysis of patients who did not receive 70% or more of the planned dose makes interpretation of these data difficult. No analysis based on intention to treat was performed in this study.

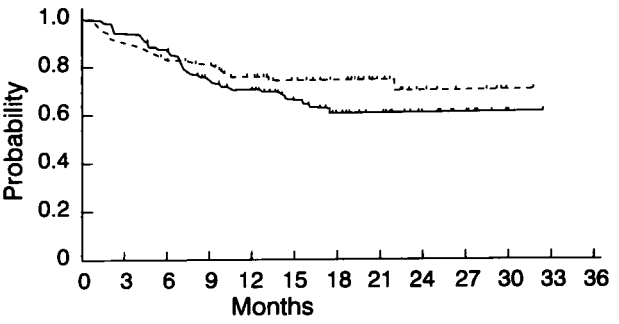

Figure 4. Time to treatment failure for patients receiving COP-BLAM chemotherapy for NHL supported by GM-CSF (solid line) or placebo (broken line). Reproduced with permission from Gerhartz HH, Engelhard M, Meusers P, *et al.* Randomized, double-blind, placebo-controlled, phase III study of recombinant human granulocyte-macrophage colony-stimulating factor as adjunct to induction treatment of high grade malignant non-Hodgkin's lymphomas. *Blood* 1993; **82**: 2329–2339.

In another study from Manchester, patients with intermediate/high-grade NHL receiving weekly alternating chemotherapy with VAPEC-B (vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin) were randomised to receive either G-CSF or control.[24] The use of G-CSF was associated with a lower incidence of neutropenia (37% vs 81%), neutropenic fever (22% vs 44%), and chemotherapy dose reduction (10% vs 33%). Received dose intensity was higher in G-CSF treated patients, with no increase in toxicity, except for neutropenia.

However, response rates were identical in G-CSF and control patients (90% vs 92%) and there was no difference in DFS or OS between the two groups.

Many more prospective studies of growth-factor supported chemotherapy are currently in progress in leukaemia and lymphoma, using several cytokines including G-CSF, GM-CSF, IL-3, stem cell factor (SCF) and various growth factor combinations. Their results are awaited with interest. The advent of recombinant thrombopoietin is likely to have significant impact on chemotherapy-induced thrombocytopenia, and its use may allow further dose intensification.[25]

Current evidence suggests that haemopoietic growth factors facilitate adherence to dose and schedule, and reduce myelosuppression, at least in patients receiving combination chemotherapy for lymphoma. Whilst retrospective analyses suggest

Table 1. Chemotherapy doses of BEAM and mini-BEAM

	BEAM (mg/m^2)	mini-BEAM (mg/m^2)
Carmustine	300	60
Etoposide	800	300
Cytosine arabinoside	1600	800
Melphalan	140	30

Reproduced with permission from Linch DC, Winfield D, Goldstone AH, *et al.* Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341**: 1051–1054. © 1993 The Lancet Ltd.

that improved dose adherence is associated with improved outcome, this has yet to be confirmed in the setting of randomised clinical trials.

The role of high-dose therapy in haematological cancer

High-dose therapy, with bone marrow or peripheral blood progenitor cell rescue, is probably the most widely used strategy for dose intensification in patients with haematological malignancy. Although initially used only for patients with relapsed or refractory disease, improvements in patient selection and supportive care, plus the advent of PBPCT, have allowed the use of high-dose therapy as a component of first-line treatment of haematological cancer.

As with other dose-intensive approaches, much published data is from single-institution phase II studies, or from retrospective, registry-based analyses. Selection, referral and reporting bias may therefore exist in the patient populations in these studies. However, early results from prospective studies are now emerging and suggest that, at least in some situations, dose intensification above the conventional dose range may produce higher response and survival rates.

High-dose therapy for salvage of relapsed/refractory patients

Hodgkin's disease

The results of conventional-dose salvage chemotherapy for patients with relapsed/refractory Hodgkin's disease after first-line combination chemotherapy are poor, and are influenced by the duration of first remission. In the series from the NCI, patients retreated with MOPP after initial MOPP failure achieved a 93% CR rate if the initial remission duration was greater than one year, compared with 29% if it was less than one year.[26] Even in the more favourable group, the long-term OS was only 24%. Similar results have been reported from Milan, where patients initially treated with MOPP, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or MOPP/ABVD received similar regimens or non-cross resistant regimens at relapse.[27] Patients relapsing more than one year after initial therapy had a 5-year FFR of 51% compared with only 20% in those with early relapse. Patients with primary refractory disease in this and most other series rarely achieve long-term RFS.

The results using high-dose therapy and autologous stem cell transplantation (ASCT) in single-institution studies have generally been superior to conventional-dose salvage.

In a report from Nebraska and the MD Anderson Cancer Center, 128 patients with relapsed Hodgkin's disease received CBV (cyclophosphamide, carmustine, etoposide) with ASCT.[28] The 4-year actuarial OS for the entire group was 45%, with a corresponding progression-free survival (PFS) of 25%. Similar results have been reported in several other studies. Patient selection for high-dose salvage therapy may well be an important determinant of outcome in these single-institution studies.

A single prospective randomised study has been conducted by the British National Lymphoma Investigation (BNLI).[29] In this trial 40 patients with relapsed/refractory Hodgkin's disease were randomised to receive either BEAM (carmustine, etoposide, Ara-C, melphalan) with autologous bone marrow transplantation (ABMT), or a lower-dose (but still dose-intensive) combination, 'mini-BEAM'. Both combinations were administered over a 5-day period, the total doses in each being as summarised in Table 1.

The 3-year actuarial event-free survival was 53% in the BEAM group vs 10% in the mini-BEAM group ($p = 0.025$) (Figure 5). The progression rate was significantly lower in the BEAM group. However, although there was a trend for superior survival in the high-dose group, this did not reach statistical significance. The results of this trial suggest a possible advantage of dose intensification to myeloablative levels in these patients, although the patient numbers are small and the authors do not provide details of the first-line therapy in these patients. This may have had a substantial effect on the results of second-line therapy.

A larger randomised study of intensive 'conventional-dose' salvage vs high-dose salvage with ASCT is currently in progress in Germany.

Non-Hodgkin's lymphoma

As with Hodgkin's disease, results of conventional-dose salvage chemotherapy in patients with intermediate/high-grade NHL are poor, with median survival duration of 6–9 months in most series, and only 10%–15% of patients achieving long-term DFS.[30–32] Numerous published series of high-dose salvage with ASCT have reported superior outcome, especially for patients whose disease is still responsive to conventional-dose therapy given prior to high-dose treatment.[33,34] However, the apparent superiority of high-dose therapy has only recently been tested in a randomised clinical trial. In the PARMA international study, patients with relapsed/refractory intermediate-grade NHL were treated with two cycles of conventional-dose salvage therapy using DHAP (dexamethasone, high-dose Ara-C, cisplatin).[35] Responding patients were randomised to receive either four further cycles of DHAP, or high-dose chemotherapy with BEAC (carmustine, etoposide, Ara-C, cyclophosphamide). Results from this study will be reported shortly, although preliminary results suggest a benefit from high-dose chemotherapy.

For patients with high-grade (diffuse small non-cleaved cell and lymphoblastic) lymphoma, small single-centre studies and registry data have suggested that high-dose therapy produces superior OS and DFS compared with conventional-dose salvage.[33,36] No comparative data are available, and prospective studies are not feasible in these rare diseases. High-dose therapy is therefore recommended for salvage therapy of these diseases, although its effect on outcome is unclear.

Acute myeloid leukaemia

AML was one of the first conditions in which high-dose therapy with allogeneic bone marrow transplantation was first used, in patients who had failed conventional-dose therapy.[37] Long-term survival was observed in about 10% of the original patients treated in Seattle, providing some of the earliest evidence that dose intensification to this level could improve DFS and OS. In previous studies of conventional-dose chemotherapy after relapse from first remission, only 50% of patients achieved a second CR, and the median duration of second CR was only 4–6 months.

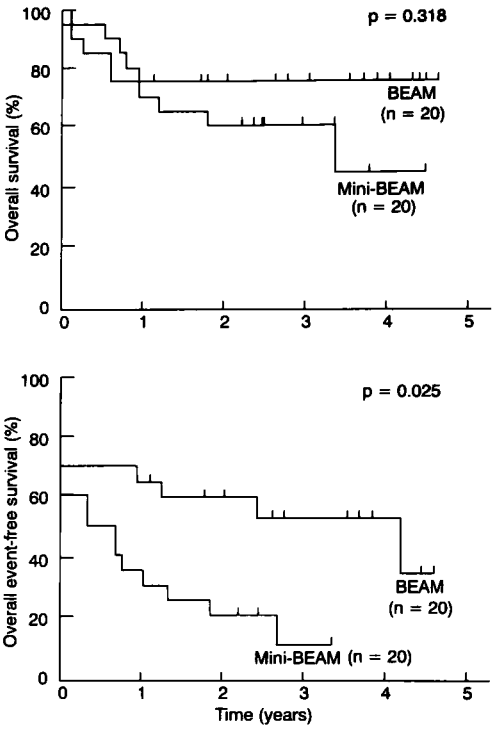

Figure 5. Overall survival (upper figure) and event-free survival (lower figure) for patients with relapsed Hodgkin's disease treated with BEAM or mini-BEAM. Reproduced with permission from Linch DC, Winfield D, Goldstone AH, *et al.* Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341**: 1051–1054. © 1993 The Lancet Ltd.

In a recent study from Seattle, 126 patients with AML treated with high-dose therapy and allogeneic BMT in untreated first relapse were reported.[38] The actuarial 5-year relapse-free survival for this group was 23%. In a smaller series, Petersen *et al.* have reported 47 patients treated with high-dose therapy and ABMT in untreated first relapse, or second CR.[39] The 2-year actuarial relapse-free survival was 45% for patients in untreated relapse, and 32% for those in second CR.

These results are superior to those for conventional-dose therapy, but no randomised comparative trials exist to confirm this observation.

High-dose therapy as a component of initial therapy

Improvements of supportive care for patients receiving high-dose therapy and particularly PBPCT[40] have resulted in several studies addressing the role

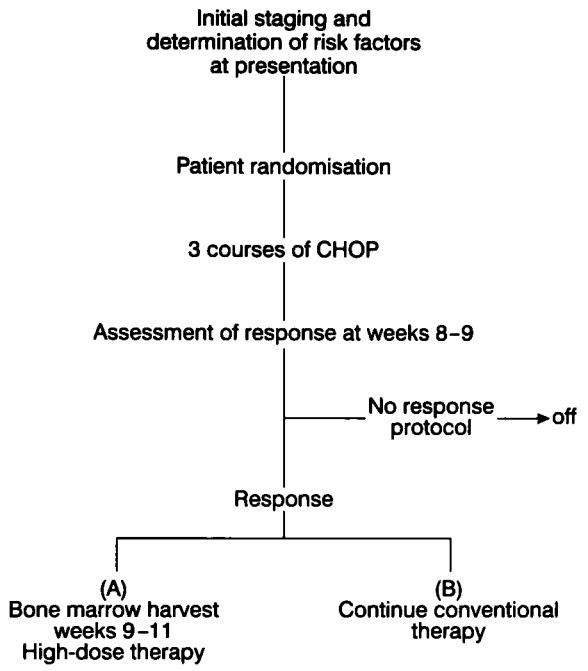

Figure 6. Schema of protocol for UK study of first remission high-dose therapy in intermediate/high-grade NHL.

Table 2. Survival rates for patients with NHL according to risk group as defined by the International Prognostic Factors Project

Risk group	Number of risk factors *	5-year overall survival (%)
Low	0 or 1	73
Low intermediate	2	51
High intermediate	3	43
High	4 or 5	26

* Risk factors: age (≤ 60 vs > 60), stage (I/II vs III/IV), serum LDH (normal vs elevated), performance status (0,1 vs ≥ 2), number of extranodal sites (0,1 vs ≥ 2). Reproduced with permission from the International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *New Engl J Med* 1993; **329**: 987–994. © 1993 The Massachusetts Medical Society.

of high-dose therapy as a component of first-line treatment of haematological cancer.

Non-Hodgkin's lymphoma

The role of high-dose therapy with PBPCT in first remission in intermediate and high-grade NHL has been the subject of relatively few studies, most of which have reported encouraging results. In a study from Stanford University, 20 patients with intermediate/high-grade NHL received high-dose therapy with ABMT.[41] All were classified as 'poor risk'. The 3-year actuarial DFS for patients in this series was 84%. Comparable results have been reported from three other studies.[42–44] A retrospective analysis from the EBMT reported a 5-year actuarial DFS of 70% for 102 patients with intermediate or high-grade NHL receiving ABMT in first complete remission.

Although these results are encouraging, they are difficult to interpret due to variability in patient selection, particularly with respect to prognostic factors. Furthermore, even with conventional chemotherapy alone, the long-term DFS for patients who achieve a CR with conventional-dose therapy is around 70% in most series. It is therefore unclear whether high-dose therapy administered to consolidate first CR improves long-term outcome.

The issue of prognostic factors and selection of poor-risk categories has been addressed recently in a large collaborative study of over 3000 patients with aggressive NHL.[45] A predictive model has been developed which identifies various risk groups (Table 2). Recently-initiated studies have used this prognostic model, selecting those patients with high-risk and high/intermediate-risk disease for early intensification of therapy. A UK Lymphoma Group/EBMT study is underway in which poor-risk patients identified using this model receive three cycles of CHOP chemotherapy. Responding patients are then randomised between three further cycles of CHOP, or high-dose therapy and ASCT (Figure 6).

In a similar study, the GELA group in France have compared high-dose therapy and ABMT with consolidation sequential chemotherapy at 'conventional' dose for 'poor-risk' patients entered onto the LNH 84 protocol.[46] A total of 464 patients were evaluable. With a median follow-up of 28 months, the 3-year DFS for the sequential chemotherapy arm was 52%, compared with 59% for the high-dose arm ($p = 0.46$). No difference in outcome was achieved with dose intensification in this group.

The treatment of lymphoblastic lymphoma in adults presents similar problems of interpretation. Phase II and registry-based studies of dose intensification with high-dose therapy and ASCT in first remission have produced superior results to those achieved for 'poor-risk' patients treated with conventional-dose regimens.[36,47] The influence of patient selection on outcome in these series has been difficult to determine, and a randomised study is now in progress, comparing conventional consolidation therapy with high-dose therapy and ASCT.

High-dose sequential therapy

The use of high-dose sequential therapy represents a further strategy for increasing dose intensity, using marrow or PBPC support. There are only a few published studies of this approach at present. High doses of non-cross resistant drugs are administered sequentially over a relatively brief duration, achieving high-dose intensity but with less theoretical potential for acquired drug resistance. Although the drugs are administered at sub-myeloablative doses, bone marrow or PBPC support is given to hasten haemopoietic recovery. Most current protocols use PBPCs mobilised using chemotherapy and haemopoietic growth factors—most commonly G-CSF and GM-CSF.

Gianni *et al.* have used a high-dose sequential regimen for poor-prognosis patients with relapsed Hodgkin's disease.[48] In their most recent report, the event-free survival at 6 years for the 25 patients in the series was 78% for those with an initial remission duration of less than one year, and 31% for those with disease which was primarily refractory to MOPP/ABVD.[49] These are encouraging phase II results, but require prospective evaluation. Recent high-dose sequential approaches have used multiple cycles of dose-intensive chemotherapy supported by PBPCs mobilised into the blood by haemopoietic growth factors, using whole blood rather than leukapheresis products as the source of haemopoietic rescue.[50] It is likely that this approach will gain increasing use and allow further investigation of the role of dose-intensive therapies in these diseases.

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