Cancer Chemother Pharmacol (1997) 40 (Suppl): S110–S114

ORIGINAL ARTICLE

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Chemotherapy: the more, the better in malignant lymphoma?

Abstract Several clinical trials have demonstrated that high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation is more effective than conventional-dose chemotherapy in some subsets of patients with malignant lymphoma, such as relapsed aggressive lymphoma patients showing a response to salvage chemotherapy and those with Hodgkin's disease who fail primary initial chemotherapy. This paper summarizes recent findings and the following issues remaining to be resolved: (1) whether HDC is superior to conventional-dose chemotherapy as initial therapy for aggressive lymphoma in unfavorable risk groups, (2) whether single HDC or multiple semi-HDC is better, (3) whether HDC has curative potential in indolent lymphoma or mantle-cell lymphoma, and (4) the HDC regimen that is most useful. To clarify these controversial issues, well-designed clinical trials are needed. To evaluate whether the concept "the more chemotherapy, the better in malignant lymphoma" is valid, the Lymphoma Study Group of the Japan Clinical Oncology Group is conducting two kinds of clinical trials in high- and high–intermediate-risk aggressive lymphoma patients, focusing on the dose intensity of key agents. One is a randomized phase II trial of dose-escalated cyclophosphamide, doxorubicin, vincristine, and prednisolone (high CHOP) versus shortened CHOP (biweekly CHOP) with prophylactic use of granulocyte colony-stimulating factor. The other is a phase II trial of HDC with peripheral blood stem-cell transplantation as a part of the initial therapy. If promising results are obtained from these trials a randomized phase III trial will be considered to compare the best dose-intensive regimen with standard CHOP.

Key words Dose intensity · High-dose chemotherapy · Autologous hematopoietic stem-cell transplantation · Granulocyte colony-stimulating factor

Work presented at the 12th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New therapeutic strategies for higher cure rates: High-dose therapy and new therapeutic modalities," 4–5 October 1996, Nagoya, Japan

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Introduction

In cancer chemotherapy the concept of "the more, the better" has been one of the most controversial issues. In general, anticancer agents are directly toxic to tumor cells, and the degree of tumor-cell killing is usually proportional to the dose and the duration of exposure. Several preclinical studies demonstrated that there was a steep linear-log dose-response relationship for alkylating agents, anthracyclines, and platinum compounds but not for antimetabolites [6]. The dose-limiting toxicity (DLT) of most anticancer agents is myelotoxicity. If the myelotoxicity of anticancer agents with a steep dose-response relationship could be ameliorated, the dose of such anticancer agents could probably be escalated and their antitumor effects potentiated.

Combination chemotherapies against aggressive lymphoma

Malignant lymphoma is one of the most chemosensitive neoplasms, and a number of anticancer agents have demonstrated antitumor effects. Since DeVita et al. [4] reported the curative potential of the nitrogen mustard, vincristine, procarbazine, and prednisolone (MOPP) regimen in patients with Hodgkin's disease, a tremendous number of combination chemotherapy regimens for use in Hodgkin's disease and non-Hodgkin's lymphoma (NHL) have been reported. In chemotherapy for NHL of aggressive histology (intermediate- and high-grade histology), according to the Working Formulation [18], cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [17] and CHOP-

like regimens [15, 22] are standard combination chemotherapy regimens.

Since the late 1970s, on the basis of the Goldie-Coldman hypothesis [9] the development of "non-cross-resistant, alternating combination chemotherapy regimens" such as methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (M-BACOD) and prednisone, doxorubicin, cyclophosphamide, and etoposide (ProMACE)-MOPP has been reported. These regimens included bleomycin, methotrexate, procarbazine, and cytosine arabinoside, which were expected to be non-cross resistant to the agents in the CHOP regimen. These are called second-generation chemotherapies, whereas CHOP and CHOP-like regimens are called first-generation chemotherapies.

Thereafter, promising results of "the third-generation chemotherapies" such as methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) and prednisone, doxorubicin, cyclophosphamide, and etoposide followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM) were reported. These regimens were devised to intensify the relative dose intensity by shortening the therapeutic duration using multiple anticancer agents, similarly to the second-generation regimens. However, subsequent multicenter phase II studies could not reproduce the initially positive results of single-institution studies of M-BACOD, ProMACE-CytaBOM, and MACOP-B.

First-generation CHOP revisited

Several large-scale, prospective randomized phase III studies comparing second- or third-generation regimens with CHOP revealed that these regimens were equivalent to CHOP in terms of therapeutic efficacy but were more expensive and more toxic [3, 5, 10]. Therefore, most oncologists currently consider CHOP to be the gold standard.

Several reasons to explain the failure of the second- and third-generation strategies have been proposed. Probably the most important is that the dose intensity of key agents such as cyclophosphamide and doxorubicin achieved in these regimens is lower than that reached in CHOP. If the dose intensity of key agents is a significant determinant of the therapeutic outcome, as the Stanford group has indicated on the basis of multivariate analysis [14], the second- and third-generation chemotherapy regimens would not be appropriate methods to evaluate the concept of the more, the better. Patient selection, small sample sizes, and short follow-up duration might also explain the initial false-positive results. In 1993 the International Non-Hodgkin's's Lymphoma Prognostic Factors Project [13] revealed that there were significantly heterogeneous prognostic subsets among aggressive lymphoma patients. Therefore, we must readdress the issue of the more, the better taking the prognostic subsets into consideration.

High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in relapsed aggressive lymphoma

The most effective method to ameliorate the myelotoxicity of anticancer agents is autologous hematopoietic stem-cell transplantation (AHSCT). Malignant lymphoma is one of the neoplasms in which the therapeutic efficacy of high-dose chemotherapy (HDC) with AHSCT has been extensively investigated [1, 20]. Several clinical trials have demonstrated that HDC is a promising treatment modality in relapsed aggressive lymphoma patients who have responded to salvage chemotherapy [20]. In 1995 the first international prospective randomized study comparing HDC with autologous bone marrow transplantation (ABMT) and conventional-dose salvage chemotherapy was reported [21]. This study clearly demonstrated overall and event-free survival rates that were significantly higher after HDC than after conventional-dose chemotherapy.

The therapeutic efficacy of HDC with AHSCT has also been extensively investigated in Hodgkin's disease [2]. Several single-arm phase II studies suggested that HDC was superior to conventional-dose salvage chemotherapy in patients with Hodgkin's disease who failed initial therapy, and the most compelling evidence for the superiority of HDC in such patients was reported by the British National Lymphoma Investigation [16]. This was the first randomized comparison of HDC with conventional-dose chemotherapy in relapsed or refractory Hodgkin's disease, and it showed that the actuarial 3-year event-free survival rate was significantly better in patients who received HDC (53% versus 10%). This study was closed early because patients refused to be randomized. Thus it appears that the superiority of HDC with AHSCT has been confirmed in patients with chemotherapy-sensitive aggressive lymphoma in relapse and those with Hodgkin's disease who fail initial chemotherapy.

HDC with AHSCT as initial chemotherapy in poor-prognosis aggressive lymphoma

After randomized studies had documented the superiority of HDC in patients with aggressive lymphoma or Hodgkin's disease in relapse, many investigators proceeded to conduct clinical trials to investigate the effectiveness of initial HDC for aggressive lymphoma patients with poor prognosis. The results of at least four prospective randomized trials addressing this important issue have been reported. The first study was a French multicenter randomized trial comparing HDC and ABMT with sequential chemotherapy in poor-prognosis aggressive lymphoma [11]. A poor prognosis was defined as the presence of at least one of the following unfavorable prognostic factors: an Eastern Cooperative Oncology Group performance status of 2–4; the presence of two or more extranodal sites, and a tumor burden measuring $\geq$10 cm in the largest dimension. In this study, patients who achieved a complete remission with induction

Table 1 Findings and controversial issues regarding HDC with AHSCT in malignant lymphoma

Findings:
1. HDC is more effective than salvage chemotherapy with a conventional dose in relapsed patients with chemotherapy-sensitive aggressive lymphoma
2. Most rapid hematologic recovery after transplantation is achieved in patients undergoing peripheral blood stem-cell rescue than in patients receiving ABMT
3. HDC is probably superior to salvage chemotherapy with a conventional dose in the treatment of patients with Hodgkin's disease in whom primary chemotherapy fails or initial remission is brief
Controversies:
1. Is HDC superior to conventional-dose chemotherapy as an initial therapy for aggressive lymphoma patients in unfavorable risk groups?
2. To obtain more potent antitumor effects, is single HDC or multiple semi-HDC better?
3. Does HDC have curative potential in patients with indolent lymphoma or mantle-cell lymphoma?
4. Which HDC regimen is the most effective?
5. Is in vitro purging of lymphoma cells or $CD34^+$ selection of harvested hematopoietic stem cells a useful method of decreasing the relapse rate after transplantation?
6. Is there a role for allogeneic peripheral blood stem-cell transplantation in the treatment of malignant lymphoma?

chemotherapy were further randomly assigned to receive one of two consolidation procedures. It was concluded that consolidation with HDC and ABMT was not superior to conventional-dose chemotherapy. However, at the Lugano Conference in June 1996 the updated results of this trial were reported [12]. The researchers reanalyzed the survival data according to the International Index and found that the 5-year disease-free survival rate was significantly higher in the ABMT arm (57% versus 36%, $P = 0.01$). However, these are not confirmatory data because this was a subset analysis.

The second prospective randomized study to examine the role of the early administration of HDC was reported by a Dutch group [25]. In this study, 69 slow responders, defined as having achieved only a partial response after three courses of CHOP, were randomized. The patients assigned to the ABMT arm were treated with high-dose cyclophosphamide (60 mg/kg given for 2 days) and total-body irradiation (800 cGy given in one fraction), and those assigned to the CHOP arm received an additional five courses of CHOP. The overall and event-free survival rates obtained in the ABMT arm were inferior to those obtained in the CHOP arm, although not significantly so. The patients who responded slowly to CHOP did as well as those who responded rapidly. In addition, reanalysis using the International Index revealed that more than half of the randomized patients could be classified into low- or low-intermediate-risk groups. Therefore, the most significant problem in this study was inappropriate patient populations.

The third randomized study was a multicenter Italian study that compared HDC with AHSCT against a third-generation regimen, MACOP-B [7]. It was concluded that the 7-year results in the high-dose arm were superior to those in the MACOP-B arm, although the HDC regimen was unique and very complicated [high-dose cyclophosphamide (day 0) followed by vincristine and high-dose methotrexate with leucovorin rescue (day 21), followed by high-dose etoposide (day 34), and finally by total body irradiation plus melphalan with AHSCT (day 60)].

The fourth randomized trial was reported by a French group at the Lugano Conference [8]. In this study a short-term high-intensity treatment in combination with AHSCT on day 60 was used to increase the response rate, and 302 high- and high–intermediate-risk aggressive lymphoma patients (according to the age-adjusted International Index) were randomized either to this treatment or to doxorubicin, cyclophosphamide, vindesine, and prednisone (ACVB). Short-term intensive treatment with AHSCT was significantly inferior to conventional-dose chemotherapy in terms of overall and event-free survival.

Although several randomized trials have been reported, it is very difficult to draw a definitive conclusion regarding the role of the early administration of HDC. The four major differences in the randomized studies reported are: (1) the patient selection criteria, (2) the HDC regimen, (3) the timing of HDC, and (4) the standard-dose regimen. To address this important issue properly, carefully designed clinical trials are needed.

Remaining controversial issues regarding HDC

The findings and the controversial issues regarding HDC are summarized in Table 1. The following issues remain unresolved: whether single HDC or multiple semi-HDC is better, whether HDC has curative potential in indolent lymphoma or mantle-cell lymphoma, and the HDC regimen that is most effective. To clarify these controversial issues, more well-designed clinical trials must be conducted.

Clinical trials conducted by the Lymphoma Study Group of the Japan Clinical Oncology Group

The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) has conducted consecutive multicenter clinical trials of regimens for the treatment of

Table 2 Treatment scheme used in JCOG9505, a randomized phase II study comparing biweekly CHOP with high CHOP in high- and high-intermediate-risk aggressive lymphoma patients[a] (*div* Drip i.v. infusion, *G-CSF* granulocyte colony-stimulating factor)

Regimen	Drug	Dose	Days of administration
Biweekly CHOP (LSG19)	Cyclophosphamide	750 mg/m² div	1
	Doxorubicin	50 mg/m² div	1
	Vincristine	1.4 mg/m² i.v. (maximum 2.0 mg)	1
	Prednisolone	100 mg p.o.	1–5
	G-CSF	2 μg/kg s.c.	3–(13)
	Eight cycles were given with an interval of 2 weeks between cycles		
High CHOP (LSG20)	Cyclophosphamide	1500 mg/m² div	1
	Doxorubicin	70 mg/m² div	1
	Vincristine	1.4 mg/m² i.v. (maximum 2.0 mg)	1
	Prednisolone	100 mg p.o.	1–5
	G-CSF	2 μg/kg s.c.	3–(20)
	Seven cycles were given with an interval of 3 weeks between cycles		

[a] The primary end point is response

Table 3 Treatment scheme for JCOG9506, a phase II study of HDC with autologous hematopoietic stem-cell rescue in high- and high-intermediate-risk aggressive lymphoma patients[a] (*div* Drip i.v. infusion, *G-CSF* granulocyte colony-stimulating factor)

Drug	Dose	Days of administration
Initial chemotherapy (biweekly CHOP):		
Cyclophosphamide	750 mg/m² div	1
Doxorubicin	50 mg/m² div	1
Vincristine	1.4 mg/m² i.v. (maximum 2.0 mg)	1
Prednisolone	100 mg p.o.	1–5
G-CSF	2.5, 10 μg/kg s.c.	3–(13)
Four to six cycles were given with an interval of 2 weeks between cycles		
HDC with autologous hematopoietic stem-cell rescue:		
Dexamethasone	25 mg/m² div	–7 to –3
Carboplatin	200 mg/m² div	–7 to –3
Etoposide	250 mg/m² div	–7 to –3
Cyclophosphamide	1200 mg i.v.	–7 to –3
Mesna	120% of cyclophosphamide dose	–7 to –3
Stem-cell rescue		0– (1)
G-CSF	5 μg/kg s.c.	1

[a] The primary end point is survival

aggressive lymphoma [22–24]. We have also investigated the second- and third-generation multiagent strategies [24]. However, on the basis of the results of large-scale randomized studies conducted in Western countries [3, 5, 10], we changed our strategy from multiagent chemotherapy to dose-intensive chemotherapy focusing on key agents.

To address the concept of the more, the better in malignant lymphoma the JCOG-LSG is conducting two kinds of clinical trials in high- and high-intermediate-risk (according to the International Index) aggressive lymphoma patients. One is a randomized phase II trial of dose-escalated CHOP (high CHOP) versus shortened CHOP (biweekly CHOP) with prophylactic use of granulocyte colony-stimulating factor. The treatment scheme of JCOG9505 (LSG19 versus LSG20) is shown in Table 2. The dose and the schedule for high CHOP were determined on the basis of the results of a combination phase I/II study [19], and the primary end point is response.

The other study is a phase II trial of HDC with peripheral blood stem cell rescue as a part of the initial therapy. The treatment scheme of JCOG9506 (LSG18) is shown in Table 3. In this study, high- and high-intermediate-risk (according to the age-adjusted International Index) aggressive lymphoma patients were eligible. They receive HDC followed by autologous peripheral blood stem-cell transplantation after four to six cycles of biweekly CHOP. If promising results are obtained in these trials, a prospective randomized phase III trial will be considered to compare the best dose-intensive regimen with standard CHOP.

Acknowledgements This study was supported in part by Grants-in-Aid for Cancer Research (7–29, 8S–1) from the Ministry of Health and Welfare, Japan. I thank the many physicians who have participated in the various clinical trials conducted by the JCOG-LSG.

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