Symposium article

The CUP trial: A randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL)

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Summary

Background: The CUP trial was initiated to analyze the value of high-dose therapy and stem-cell transplantation and purging in patients with relapsed chemosensitive follicular NHL.

Patients and methods: After three cycles of chemotherapy responsive patients were randomized to either three more cycles of the same chemotherapy (C), high-dose therapy followed by autologous unpurged (U) or purged (P) stem-cell transplantation. Purging was performed using a cocktail of monoclonals. Pretransplant conditioning consisted of cyclophosphamide (60 mg/kg x 2) and total body irradiation.

Results: Of the 140 patients registered from 26 centers in Europe, 89 fulfilled the criteria for randomization (C: 24, U: 33 and P: 32). Reasons for failure to randomize were: no response (28), persistent marrow infiltration (4), patient refusal (7), other (7), no data (5). With the current follow up (median 26 months from randomization) 16 (66%) in C are known to have progressed or relapsed, in contrast to 13 (39%) of U and 12 (37%) of the P patients (P-value 0.002). Overall survival is premature with the current available data.

Conclusions: Patients in U and P arms had higher progression/relapse-free survival rate. There are some suggestions of some improvement in overall survival rate.

Key words: follicular lymphoma, high-dose therapy, purging, randomized trial

Introduction

About one-third of all patients with non-Hodgkin's lymphoma have a follicular histology. The majority of these patients have stage III or IV disease at diagnosis and a median age of more than 50 years.

Although chemotherapy can induce complete remissions, eventually almost all patients will relapse. The available survival curves do not show any evidence of a plateau, suggesting cure, although the median survival may be between 4 and 10 years [1].

There are now substantial data on patients treated with high-dose chemotherapy followed by stem-cell transplantation, however, the results from these studies are hampered by insufficient numbers or follow-up [2-15]. Randomized studies have not been done. Although promising there is no evidence that treatment with high dose therapy followed by stem-cell transplantation may be beneficial for the patient.

Patients with follicular non-Hodgkin's lymphoma have frequently bone marrow infiltration. Therefore, there are some arguments that if high dose therapy is considered in the treatment plan of a patient purging of the graft may be necessary. The first results from Gribben et al. [16], although not obtained from a controlled randomized study, do support purging.

To answer the questions on efficacy of high-dose therapy and purging in patients with follicular non-Hodgkin's lymphoma, a randomized trial was initiated comparing standard chemotherapy with high-dose therapy followed by unpurged stem-cell transplantation or high-dose therapy followed by purged stem-cell transplantation (CUP trial).

Patients and methods

Patients were treated with three cycles of chemotherapy. The choice of chemotherapy was free, although CHOP chemotherapy was recommended. In case of a response after three cycles of chemotherapy, defined as at least partial response according to standard criteria and minimal B-cell infiltration of the marrow (less than 20% B lymphocytes) patients were eligible for randomization. From the beginning patients were randomized between three arms (CUP trial), starting June 1996, patients and doctors also had the choice for a two arm randomization (transplantation with unpurged or unpurged stem cells (UP trial) (Figure 1).

Stem cells (either blood or bone marrow) were collected as soon as possible after randomization.

Patients randomized to the purging arm had their stem cells purged with a cocktail of anti-CD19, anti-CD20, anti-CD22, anti-CD23 and anti-CD37 plus immunomagnetic beads [17] (supported by Baxter Immunotherapy).

Patients randomized to the chemotherapy arm were treated with three more cycles of the same chemotherapy. Patients in the stem-cell transplantation arms were treated with high dose cyclophosphamide (2 x 60 mg/kg) followed by TBI and stem-cell transplantation.
The trial aimed for 100 patients in every randomization arm. However, because of poor accrual the trial was closed for entry in April 1997.

Results

A total of 140 patients were entered in the study of whom 89 fulfilled the criteria for randomization. The baseline characteristics are shown in Table 1. Reasons for failure to randomize were no response ($n = 28$), persistent marrow infiltration ($n = 4$), refusal ($n = 7$), other ($n = 7$), no data ($n = 5$). Twenty-four patients were randomized to the chemotherapy arm, thirty-three were treated with high-dose therapy and transplanted with unpurged stem cells and thirty-two patients with purged autologous stem cells.

This initial analysis reports results two years after the study was closed to patients entry. The median of follow-up time from randomization was 26 months. The Kaplan-Meier plot for progression or relapse free survival is displayed in Figure 2. With the current follow up, 16 (66%) of patients in the chemotherapy arm have...
progressed or relapsed in contrast to 13 (39%) of the unpurged patients and 12 (37%) of the purged patients. The $P$-value of log-rank test is $P = 0.002$. The hazard ratio of pairwise comparison is summarized in Table 2.

Overall survival analysis is premature, but the results to date can be seen from the survival curves in Figure 3. The $P$-value of log-rank test is equal to 0.08. With the current available data, the estimated three-year survival rate is 68%, 70% and 90% in the chemotherapy, unpurged and purged arms, respectively.

Discussion

This is the only randomized trial currently ongoing in patients with relapsed follicular non-Hodgkin’s lymphoma assessing the value of high-dose therapy and purging. Since the trial has started to accrue patients several centers have initiated transplantation of patients with a relapsed follicular lymphoma, although data supporting this decision are not convincing. This trend has increased after the general implementation of peripheral blood stem cells with decreased morbidity and mortality. This has had a great impact on the accrual of patients in this trial, finally resulting in the premature closing of entry.

With current follow-up, which indisputably is too short...
for this low-grade disease, the results show a significantly improved progression free survival rate in the transplanted patients. Although the overall survival analysis is premature, there are suggestions of some improvement in the survival rate. We wait the long-term follow-up with interest.

*Appendix*


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