Relapsed Hodgkin's lymphoma: new twist to the standard regimen

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Results of a multicentre study show that a sequential high-dose chemotherapy variant of the standard treatment is safe and effective in relapsed Hodgkin's patients.

High-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) has been the standard care for patients with relapsed Hodgkin's lymphoma for many years, achieving better results than MINI-BEAM (low-dose carmustine, etoposide, cytarabine, and melphalan) and DEXA-BEAM (dexamethasone, carmustine, etoposide, cytarabine and melphalan) in randomised studies. However, many questions remain regarding the conduct of such a programme for relapsed and refractory disease, including the best selection of patients, optimal choice and sequencing of drugs prior to high-dose treatment, and value of allogeneic stem-cell sources.

In a large multicentre study by the German Hodgkin Lymphoma Study Group, reported by Josting et al. (see opposite), patients with primary refractory and relapsed Hodgkin's lymphoma received two cycles of DHAP (dexamethasone, high-dose cytarabine and cisplatin), and responders underwent sequential high-dose chemotherapy followed by standard and high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine and melphalan) and ASCT.

Most patients were in first relapse following primary therapy, and all patients were considered in the final analysis. Overall results of this trial were good: at 30 months, freedom from second treatment failure (FF2F) and overall survival rates were 59% and 78%, respectively. Results for FF2F were strongly affected by stage at relapse, type of remission at entry into study, and sensitivity to DHAP.

For overall survival, response to DHAP, type of remission, and presence of anaemia were strong determinants of outcome. The investigators have planned a large multicentre randomised study in which all patients with relapsed Hodgkin's lymphoma will receive two cycles of DHAP followed by either BEAM and ASCT or sequential high-dose therapy and BEAM with ASCT for patients with a complete response or partial response after DHAP.

The Goldie–Coleman hypothesis, according to which non-cross-resistant drugs should be used at lower doses in combination for initial treatment of chemo-sensitive lymphomas, has been challenged by this study. The results lend support, instead, to the Norton–Simon hypothesis, which suggests that maximum doses of sequential agents should be delivered to overcome potential resistance in patients with relapsed disease.

In general, investigators have used two methods to select patients with Hodgkin's lymphoma for ASCT. In one method, patients are induced into remission and then undergo pheresis with a regimen different from that used for induction; in the other, the same regimen is used for induction and pheresis [1,2]. Josting et al. used the former model, but with a twist: patients undergo the same type of sequential high-dose therapy for cytoreduction as employed by Gianni et al. in relapsed aggressive lymphomas and Hodgkin's lymphoma [3,4], with the added benefit of improving the quality of stem-cell products obtained.

In those reports, results were very favourable, although critics could not conclude that there was any benefit of such an approach in these single-armed trials. Nonetheless, Josting et al. have confirmed the feasibility of such a programme in a multicentre study, and have reported results in ways that strengthen support for this approach. Others have also demonstrated that this approach is feasible in therapy of follicular lymphomas and relapsed Hodgkin's lymphoma, in

The study

A. Josting et al. (2005) **Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma: results of a large multicenter study of the German Hodgkin Lymphoma Study Group**. *Ann Oncol* 16: 116–123

Background. The current treatment of choice for patients with relapsed or refractory Hodgkin's lymphoma is high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT). In line with the Norton–Simon hypothesis, sequential high-dose chemotherapy (HDSCT) – where non-cross-resistant agents are administered at brief intervals – is suggested by the authors of this study as an alternative to conventional high-dose chemotherapy in these poor-risk patients.

Objectives. To determine whether a dose-intensified and time-intensified HDSCT regimen improves outcome in patients with relapsed or refractory Hodgkin's lymphoma.

Design. This phase II study enrolled patients aged between 18 and 65 years (median age 34) with biopsy-confirmed, relapsed or progressive Hodgkin's lymphoma from 34 treatment centres in Germany. Among other criteria, eligible patients had an Eastern Cooperative Oncology Group performance status of ≤2, were free of infection and negative for HIV. All patients had undergone first-line polychemotherapy with one of a number of standard regimens, such as COPP/ABVD (cyclophosphamide, vincristine, procarbazine and prednisone, alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

Intervention. Upon relapse or progression, all patients underwent initial cytoreduction with two cycles of DHAP (dexamethasone, high-dose cytarabine and cisplatin), 14 days apart, accompanied by ondansetron on the first and second day of each cycle to minimise nausea and vomiting. Granulocyte-colony-stimulating factor was also administered to aid haematologic recovery. Patients who showed a partial response (PR) or complete response (CR) then received an HDSCT regimen comprising 4000 mg/m^2 cyclophosphamide – after which peripheral-blood stem cells were harvested by pheresis – followed by high-dose methotrexate (8000 mg/m^2), vincristine (1.4 mg/m^2), high-dose etoposide and myeloablative treatment with BEAM (carmustine, etoposide, cytarabine and melphalan). Patients then underwent ASCT. Follow-up assessments took place 100 days after ASCT, every 3 months for the first year, then every 6 months. This was reduced to once a year after 5 years.

Outcome measures. The primary endpoints were freedom from second failure (FF2F) and overall survival. Toxicity of DHAP and HDSCT were also assessed.

Results. Of the 102 patients enrolled in the study, 88% showed some degree of response (PR 67%, CR 21%) after two cycles of DHAP, and went on to receive HDSCT. After a median follow-up time of 30 months (range 3–61 months) the overall response rate was 80% (PR 8%, CR 72%), including patients who had failed after DHAP. The FF2F and overall survival for all patients were 59% and 78%, respectively. Disease progression accounted for 23 deaths (22%), and two patients (2%) died from septic shock during neutropaenia. Significant prognostic factors for FF2F were relapse status (P=0.0051), stage at relapse (P=0.0358) and chemosensitivity after DHAP (P<0.0001). Duration of first remission (P=0.0017) and anaemia at relapse (P=0.019) were significant for overall survival.

Conclusion. Salvage therapy with DHAP, followed by the prescribed HDSCT regimen, is safe and effective in patients with relapsed and refractory Hodgkin's lymphoma.

Acknowledgement. This synopsis was written by Alexandra King, *Nature Clinical Practice*.

single-armed multicentre studies [5,6]. A randomised study will be necessary to demonstrate that the FF2F achieved by Josting et al. using this approach is better than results achieved with standard methods.

Finally, questions remain over whether one could improve on these results, not only for patients with favourable relapse but also for those with unfavourable disease. Are regimens employing etoposide, gemcitabine, or other drugs better than DHAP at inducing remission? Are allogeneic stem cells useful? Will antibodies play a role in treatment? Investigators may have to utilise more novel approaches to significantly improve results for patients with recurrent Hodgkin's lymphoma.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

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First published in Nature Clinical Practice: Oncology 2005, vol 2 no.7.