Extreme Hodgkin’s lymphoma: current problem areas

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In Hodgkin’s lymphoma therapy, there remain areas of extreme difficulty. This article briefly explores these areas and provides evidence that risk-related therapy and web-based data collection programmes can facilitate progress. Unpublished data from the northern region of the UK suggest that risk-based therapy among poor-prognosis Hodgkin’s lymphoma patients aged 15–19 years is improving outcome. An index developed at the Memorial Sloan-Kettering Cancer Centre (MSKCC) for patients undergoing salvage therapy shows that new second-line regimens are urgently needed for those with poor prognosis. In primary therapy and relapse, both adolescent and adult patients with Hodgkin’s lymphoma should receive treatment tailored to their degree of risk. Elderly patients with Hodgkin’s lymphoma are also difficult to treat and fewer than 2% enter randomised clinical trials. We require new means of encouraging international pooling of data and treatment evaluation in such patients. The SHIELD project (Study of Hodgkin’s lymphoma in the Elderly Lymphoma Database; www.shieldstudy.co.uk) is now successfully providing on-line registration in the ongoing phase II study of VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisolone, mitoxantrone and bleomycin) in the elderly and guidance on obtaining ethical approval for participation.

Key words: Hodgkin’s lymphoma, prognostic index, salvage therapy, adolescent, elderly

introduction

Among children below 13 years of age, more than 95% of Hodgkin’s lymphomas are now curable. Relapse is only an occasional phenomenon and there are no subgroups in which it could be said that treatment involves extreme difficulty [1]. In the adolescent patient (aged 15–19 years), overall outcome is also generally good, with reported survival rates ranging from 70% to 90%. However, this group of patients contains some cases that are genuinely difficult to treat, namely those with bulky mediastinal nodular sclerotic disease. This fact justifies a risk-related strategy in which the poorest risk cases are managed most aggressively [2].

Adult patients aged 20–60 years with early disease can expect a greater than 95% chance of cure. Even in advanced disease, the rate of 5-year survival is 80%. However, some 10% of patients have disease that shows primary resistance towards current, standard first-line therapy or that relapses within 1 year. Patients with primary progressive and early relapsed disease represent a major clinical challenge. Another challenge in adult patients is the risk of secondary myelodysplastic syndromes, leukaemias and breast tumours. Thus, appropriately targeted therapy is important in both poor and good-risk patients, if we are to improve survival prospects and reduce the chance of adverse late events [3].

Early disease in patients aged over 60 years, if staged adequately, has a good outcome following chemotherapy and radiotherapy. However, historically, early stage disease has been over-diagnosed in this elderly population and inappropriate treatments given. Success in treating patients with advanced disease is inconsistent and the relapse rate is 70%. Overall management of the elderly patient can be regarded as extremely difficult, due, in part, to the likelihood of frailty and the presence of co-morbid conditions. In this age group, the past 15 years have seen no advance in survival [4].

patients with poor prognosis at the outset

Patients aged 20–60 years who are at high risk of primary resistance or early relapse can be identified using the numerical prognostic index developed by Proctor et al. [5]. The index, which predicts risk of death from progressive disease, is based on Ann Arbor stage, age, haemoglobin, absolute lymphocyte count and disease bulk. A score greater than 0.5 indicates poor prognosis.

In the Scottish and Newcastle Lymphoma Group’s (SNLG) validation Hodgkin’s disease (HD) study, 61% of the 101 patients with an index score greater than 0.5 had died within 4 years. Among the 336 patients with a lower score, mortality at 4 years was only 18%. The SNLG index is a better predictor of survival than stage alone and provides a firm basis for selecting patients for more aggressive therapy [5].

The index was utilised in the construction of a randomised study in the poorest-risk 20% of patients. The aim was to assess if the aggressive chemotherapy schedule PVACEBOP (prednisolone, vinblastine, adriamycin, chlorambucil, etoposide, bleomycin, vincristine, and procarbazine), with or without autologous transplant, could improve outcome in this
group. Improved outcome was demonstrated in both transplant and non-transplant approaches and was equivalent to that seen in standard risk patients [6].

A tailored approach to treatment is also needed in adolescent patients. The 1991–2002 data from the Northern NHS Region of England (population three million) provided an insight into recent management and outcome.

Over this period, 47 patients aged 15–19 years with Hodgkin’s lymphoma were treated. This represented all known cases in our population, suggesting the total for the UK as a whole in this decade was 940. Although seven of the 19 patients with early disease were treated only with radiotherapy, 12 had chemotherapy and the most frequently used regimen was ABVD. All 28 advanced disease patients had chemotherapy. As a result of having a high score on the SNLG index, 20 patients received PVACEBOP. The overall survival for the group as a whole was greater than 90%.

We recommend that patients aged less than 15 years whose prognostic index suggests high risk of resistance or early relapse should, from the outset, be candidates for treatment with state of the art chemotherapy regimens such as accelerated BEACOPP, Stanford V or PVACEBOP. They should also be assessed by PET scanning and have additional radiotherapy, if required.

Since 1988, the SNLG population study group has routinely used the prognostic index (which coincided with the introduction of PVACEBOP), three courses of chemotherapy, and radiotherapy for early-stage disease. This approach, together with the introduction of IVE (ifosfamide, etoposide and epirubicin) salvage from 1991 [7], has improved overall survival from 80% in the pre-1988 period to 87% among the 1200 patients of all stages treated since 1988.

salvage therapy

The European approach, as developed by Josting et al. [8] and collaborative groups such as the EORTC and DHSG (German Hodgkin’s Study Group), has been to give patients standard DHAP induction (dexamethasone, cytarabine, platinum) at the point of relapse and then randomise them either to further high-dose chemotherapy followed by autologous transplant, or to autologous transplant alone.

In the hands of the Cologne group, high-dose sequential chemotherapy appears to be improving outcome not only for patients who experience early or late relapse but also in primary progressive disease [8]. This latter setting is one in which second-line responses have been notoriously difficult to achieve. In a series of 75 patients treated by Josting et al. following early or late relapse after initial therapy, survival appears to have stabilised at 80% after 3 years. Among the 17 patients who had primary progressive disease, the survival plateau is around 50% and around 40% for the 10 patients who had multiple relapses.

risk adapted therapy for relapsed and refractory patients

Moskowitz and colleagues at the Memorial Sloan-Kettering Cancer Centre (MSKCC) have developed the high-dose second-line ICE regimen consisting of 5 g/m² ifosfamide, carboplatin to an AUC of 5 and etoposide 100 mg/m², with G-CSF support. Multivariate analysis showed that three factors were significant and independent predictors of poor subsequent event-free survival [9]. For extranodal disease, the hazard ratio (HR) of an event was 1.87, for B symptoms prior to ICE the HR was 1.7 and for refractory disease or relapse within a year the HR was 1.68.

ICE can produce good outcome (sustained 83% event-free survival beyond a year) in patients with one or zero adverse factors. However, patients with two factors have only a 27% chance of event-free survival beyond 2 years and 90% of patients with three adverse factors died within 1 year. Such patients desperately need novel agents and development of new forms of autologous and allogeneic transplantation which can allow salvage treatment to be tailored to prognosis.

One such strategy involves PET restaging of patients without signs of progressive disease following two cycles of ICE. Those who are PET-negative have autologous stem cell transplant of previously harvested peripheral blood progenitor cells, accompanied by BEAM (carmustine, etoposide, cytarabine, melphalan). Those who are PET-positive have 36 Gy fractionated b.i.d. involved-field radiotherapy to bulky disease. Patients with a sibling donor then undergo allogeneic stem cell transplant with BEAM. Patients with no matching donor have a tandem autotransplant, with high-dose ICE chemotherapy followed by BEAM. Studies of such approaches are continuing but require international cooperation.

encouraging clinical trials in elderly patients with Hodgkin’s lymphoma

Hodgkin’s lymphoma is eminently curable in young patients and is potentially curable in patients aged over 60 years. However, this disease in the elderly is relatively rare (with around five cases per million population per annum) and difficult to study using conventional clinical trials, partly due to patient frailty and co-morbidity. This may explain why elderly patients with Hodgkin’s lymphoma have seen no survival improvement over the past 15 years [4].

In an effort to encourage research, we have developed a web-based means of allowing individual physicians to register patients and data on their treatment using either the study protocol or an alternative. Documents designed to help prepare research applications for ethical approval can be downloaded via www.shieldstudy.co.uk.

This initiative stems from seminars held at the Cologne Hodgkin’s Lymphoma Symposium in 2001 and subsequent meetings of international groups of physicians and pathologists. This group accepted a permissive approach to treatment but recommended entry to a phase II trial of VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisolone, mitoxantrone and bleomycin). This study aimed to mirror that of Levis et al. [10] but excluded patients who are frail utilising the objective assessment criteria of co-morbidity and activities of daily living.
Due principally to changing regulations for clinical research governance within the European Union, the full launch of the programme was delayed until 2004. Since then, however, progress has been encouraging, with entry of patients and data from the UK and Germany. The German National Study Group has also been entering data on patients treated with BACOPP. Further international involvement is sought.

Planned investigations will correlate outcome with biomarkers in tissue and serum, with the aim of producing a prognostic index in the elderly. The programme also provides the opportunity to identify patients for novel therapies following relapse, such as anti-EBV T-cell immunotherapy or the use of anti-CD30 monoclonal antibodies.

An additional aim of the SHIELD programme is the development of defined palliative schedules where patients are too frail for potentially curative therapy.

**conclusion**

On-line collection of clinically relevant data linked to study protocols for treating Hodgkin’s lymphoma in elderly patients is proving efficient and feasible. It offers a paradigm for encouraging the prospective evaluation of therapies in other orphan disease areas in oncology. Hodgkin’s lymphoma in adolescence and refractory and relapsed disease in all age groups are two areas that could benefit from this web-based approach.

**references**