Strategic approach to the management of Hodgkin’s disease incorporating salvage therapy with high-dose ifosfamide, etoposide and epirubicin: a Northern Region Lymphoma Group study (UK)

Symposium article

On behalf of the Northern Region Lymphoma Group

The Northern Region Lymphoma Group is a population-based group covering 3.1 million people in Northern England. From 1991 total data collection for all Hodgkin’s disease patients for this population has been in place and it has been possible to demonstrate that the overall survival for Hodgkin’s disease for younger patients within this population has moved from 80% pre-1988 to 87% post-1988. This improvement has been brought about by the introduction of clinical trials for advanced stage disease and effective salvage regimens. This report describes the outcome of 51 patients treated with the ifosfamide, etoposide and epirubicin (IVE) schedule and includes 28 males and 23 females with a median age of 34 years. Overall 43 of 51 patients responded to treatment (84%) with 31 achieving a complete response, four a good partial response and eight a partial response. Thirty-one proceeded to autologous stem-cell transplantation. In total, with a median follow-up of 24 months (range 6–51), 26 patients remain alive and in continuous remission. Haematological toxicity, in particular neutropenia WHO grade 4, was observed in all cases but improved over the three courses of treatment. Non-haematological toxicity was not a major problem, with no significant cardiac, hepatic, renal or neurotoxicity. We conclude that the high-dose ifosfamide-containing regimens should be prospectively evaluated in the various types of non-responsive and relapsing Hodgkin’s disease.

Introduction

The treatment of Hodgkin’s disease is unequivocally a success story. Currently, with fourth-generation chemotherapy schedules, [1, 2] complete remission rates even in advanced disease exceed 90% and overall survival at 5 years is 80% for patients with advanced stage disease [1]. Outcome in early stage disease approaches 100% survival. The main aims for the next decade are to maintain or potentially improve the survival rates whilst reducing the toxicity of aggressive chemotherapeutic approaches.

In spite of progress, it is clear that 20% of patients with advanced disease will eventually fail treatment. Of this group, some 7% to 10% have primary resistance to even eight-drug schedules and further patients, in spite of initial remission, relapse early. Some relapses occur >1 year after complete remission and in these a substantial degree of chemosensitivity remains.

The Northern Region Lymphoma Group has developed a salvage therapy using high-dose ifosfamide linked to etoposide and the anthracycline epirubicin (IVE) [3], and the present report describes an update of the results with this schedule and also gives more details of the strategic approach applied to therapy of Hodgkin’s disease in a total population.

Patients and methods

In a previous study conducted between August 1992 and June 1997, 46 patients (28 male, 18 female) with relapsed or resistant Hodgkin’s disease were given treatment with IVE and have been reported elsewhere [3]. These patients included some from Scotland and Nottingham. These patients, not under our care, are not included in the present report, which does however include all patients in our region given IVE for relapsed/refractory Hodgkin’s disease.

Treatment

The salvage regimen comprised epirubicin 50 mg/m² on day 1 given as an i.v. bolus, etoposide 200 mg/m² i.v. given over 2 h on days 1 to 3 and ifosfamide 3 g/m² per day together with mesna 3 g/m² given over 22 h on days 1–3. In addition, all patients were given an i.v. bolus of mesna 1.8 g/m² prior to commencing the ifosfamide infusion and further mesna over 12 h at the completion of ifosfamide therapy. Ondansetron 8 mg bd was given as an antiemetic therapy throughout treatment in the majority of patients who also received phenytoin 300 mg orally on days –1 to day +5 as an anticonvulsant. All chemotherapy was infused by a long-term indwelling central venous catheter. It was recommended that courses be repeated every 21 days with a targeted total of three courses. Patients were not routinely given growth factor support. Toxicity was reported using WHO criteria [4] and hospital stays were defined as number of nights spent in hospital.

Transplant details

Conditioning for autotransplant and the source of stem cells was at the discretion of the individual physician, but in our region this has been with high-
dose melphalan and etoposide usually followed by non-cryopreserved marrow rescue [5].

**Response assessment**

Treatment response was assessed after the last course of IVE with full CT staging and repeat bone marrow trephines if marrow had previously been involved. A complete response (CR) was defined as disappearance of symptoms and physical signs and complete resolution of abnormalities on X-rays, scans and in the bone marrow. An unconfirmed complete response (CRu) was documented when residual mass of uncertain significance was observed. A good partial response (GPR) was defined as a disappearance of symptoms and a reduction of >75\% in measurable disease on scans and X-rays. A partial response (PR) was defined as a disappearance of symptoms and a reduction of ≥50\% in measurable disease on scans and X-rays. Survival was calculated from the date of the first IVE to September 2002 or date last known to be alive.

**Results**

Of 51 patients treated to protocol, there were 23 females and 28 males [median age 34 years (range 16–53)]. The histology comprised lymphocyte predominant Hodgkin’s disease (n = 4), mixed cellularity Hodgkin’s disease (n = 8) and nodular sclerosing subtype (n = 39). Initial therapy was doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) (n = 7), chlorambucil, vinblastine, procarbazine and prednisolone (CLVPP) (n = 20), prednisolone, vinblastine, doxorubicin, chlorambucil, etoposide, bleomycin, vincristine and procarbazine (PVACE BOP) (n = 16) and other chemotherapy (n = 9). The majority of patients were treated following first relapse, details are shown in Table 1.

Figure 1 shows overall survival by disease status at the time of receiving IVE and demonstrates, as in the previous publication and the publications of others [3, 6, 7], that in those with non-responsive disease at the end of primary therapy, only a small proportion will obtain disease control, but if this is achieved then some patients can progress satisfactorily if they proceed to additional autotransplantation. The best results in the current study are seen in the group of patients treated in first relapse, which is the largest group of patients (Table 1).

Figure 2 demonstrates survival of patients who receive the full three courses of IVE and subsequent autologous transplant, with a median survival of 46 months. Three patients who had inadequate marrow reserves received alternative transplants, two allogeneic transplants and one syngeneic, all with sustained complete remission.

**Toxicity**

All patients had grade IV haematological toxicity, but there were no treatment-related deaths. All patients developed alopecia. Nausea and vomiting was usually controlled by use of ondansetron. Ten per cent of courses were associated with WHO grade 3 infection and neurotoxicity was observed in 2\%. Oedema secondary to fluid overload was only a problem when diuretics were not given prophylactically.

| Table 1. Ifosfamide, etoposide and epirubicin regimen: Hodgkin’s disease risk categories |
|---------------------------------------------|-------------|-------------|
| No. of patients | Median survival (months) |
| <Partial response after primary therapy | 7 | 8 |
| Partial remission | 6 | 24 |
| Relapse 1 | 26 | NR |
| Relapse 2 | 7 | 46 |
| >Relapse 2 | 2 | 18 |

NR, not reached.

**Figure 1.** Overall survival post ifosfamide, etoposide and epirubicin (IVE) by status at first IVE.

**Figure 2.** Survival of patients proceeding to autologous stem-cell transplantation.
One patient developed acute myeloid leukaemia following autologous transplant. She had been transplanted following a third relapse, 8 years after her initial diagnosis.

Discussion

The Northern Region Lymphoma Group is part of the Scotland and Newcastle Lymphoma Group (SNLG), which is a population-based lymphoma organisation that aims to record data on all lymphomas in a population of 8.1 million people in Scotland and Northern England. Founded in 1979, the total population data collection programme was achieved in the total of geographical area in 1994 and has been maintained since (Figure 3). Currently, the database has over 16 000 cases of population-representative lymphoma, and this increases by 1200 new cases each year.

Since 1988 attempts have been made in this particular geographical area to create uniformed treatment approaches to apply to the whole population of patients with Hodgkin’s disease. This has included the implementation of treatment guidelines for patients with early stage Hodgkin’s disease not linked to clinical trials. For the more advanced stages, a risk-related treatment strategy for younger patients has been used which has incorporated the HD III randomised control trial using PVACE BOP + autotransplant; and this has recently been published [1]. We have demonstrated that for advanced stage poorest risk Hodgkin’s disease patients, the SNLG chemotherapy schedule has achieved a 5-year overall survival of 80%.

The strategic approach to the management of Hodgkin’s disease in younger patients is shown in Figure 4. As described in the current study, there has been increasing use of high-dose IVE for the treatment of chemotherapy failures. It is quite clear that those individuals who are resistant to current eight drug primary treatment do not achieve optimal results with second-line treatment of any kind, a fact confirmed by studies using high-dose ifosfamide linked to carboplatin and etoposide (ICE) [6]. It remains clear that novel approaches and experimental protocols

Figure 3. Scotland and Newcastle Lymphoma Group total registration.

Figure 4. Scheme for classical Hodgkin’s disease (HD) in younger patients [excluding lymphocyte predominant Hodgkin’s disease (LPHD)].
are required. Because of the small numbers involved, this will have to be done with national and international cooperation, possibly linked to biological assessments of the primary resistance therapy of this form of Hodgkin’s disease.

In the later stages of relapse all data suggest that ifosfamide-based regimens are emerging as the best form of salvage treatment, with best results seen when, after complete remission has been obtained with such regimens, some form of further intensification with stem cell rescue is given. It appears from existing data that the key element is ifosfamide, and the addition of other drugs, whether it is a platinum-based drug or anthracyclines, linked to etoposide give a very similar outcome [6, 7].

Ideally, what is now necessary is a prospective evaluation and uniform implementation of salvage approaches linked to specific risk groups for Hodgkin’s disease. Within a population-based programme, such as the SNLG, this should be possible and results could be evaluated prospectively.

Outcome in younger patients with Hodgkin’s disease is now excellent, with a 5-year survival of >80%. For older patients, outcome has not improved since the mid-1970s [8, 9]. Patients aged >60 years comprise 20% of the total population with Hodgkin’s disease and we feel that this remains the last great challenge in the treatment of Hodgkin’s disease. An international programme is under preparation to provide a framework for a study introducing risk-related therapy for this age group.

Disclosure

The authors have not reported any financial relationship with companies whose products are mentioned in the text.

References