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Alpha Interferon Maintenance Therapy in Patients with Low-Grade Non-Hodgkin's Lymphomas after Cytoreductive Chemotherapy with Prednimustine and Mitoxantrone

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A combination of prednimustine 100 mg/m²/day orally, days 1-5, and mitoxantrone 8 mg/m²/day intravenously, days 1 and 2, was administered to 19 patients with advanced low-grade non-Hodgkin's lymphoma after failure on or relapse after standard chemotherapy. The prednimustine and mitoxantrone (PmM) regimen was repeated every 4-6 weeks to a maximum of six cycles. Thirteen patients, achieving a complete (4) or partial (9) remission (CR or PR), received two additional courses for consolidation followed by interferon alfa-2b 5 million units (MU) subcutaneously (s.c.) three times weekly until progression or relapse. At the present time, remission duration ranges from 4.5+ to 17.5+ months, with a median of 14.5 months. In a historical comparison to unmaintained first remission preceding the PmM/interferon trial, a tendency towards a longer period of freedom from progression was apparent in the 13 patients receiving interferon maintenance treatment during their second PR or CR. These data provided the basis for a currently ongoing multicentre study randomly comparing initial chemotherapy with PmM versus cyclophosphamide/vincristine (Oncovin)/prednisone (COP) in patients with advanced centroblastic-centrocytic and centrocytic non-Hodgkin's lymphomas, followed by a second randomization in CR and PR patients for maintenance with alpha interferon versus observation only.
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INTRODUCTION

THE PROGNOSIS of patients with advanced low-grade non-Hodgkin's lymphomas (NHL) has remained literally unchanged over the last 50 years, with a median survival of 6-10 years from initial diagnosis [1, 2, 3]. Although most cases are responsive to a variety of cytostatic regimens, a prolongation of survival has not been demonstrated so far and most patients ultimately die from their disease. Hence, the most appropriate form of treatment still has to be defined and current therapeutic modalities range from a cautious watch-and-wait approach to intensive multi-drug regimens and even myeloablative chemoradiotherapy with subsequent bone marrow transplantation in selected subgroups of patients [4, 5, 6].

Recently, a significant anti-lymphoma activity of alpha interferon has been demonstrated by several groups, even when applied after failure to respond to cytostatic treatment. Consequently, alpha interferon was incorporated into first-line chemotherapy regimens in an attempt to improve upon remission rates and especially long-term prognosis [7, 8, 9].

Preliminary results from the various studies suggest that simultaneous administration of alpha interferon and chemotherapy does not translate into a more effective cytoreduction and a higher remission rate. Rather, an increase in treatment-associated toxicity was observed, requiring dose reduction and treatment delay.

Based on experimental data and early clinical experience, alpha interferon seems more beneficial when applied after successful initial chemotherapy with a low residual tumour burden [10]. Following this approach, the current phase II study was initiated in patients with advanced low-grade NHL after failure of standard chemotherapy, in order to explore further the potential impact of alpha interferon maintenance therapy after response to salvage treatment with the recently introduced combination of prednimustine and mitoxantrone (PmM) [11].

PATIENTS AND METHODS

The present study comprised 19 patients with advanced low-grade NHL who had failed on previous chemotherapy, including chlorambucil/prednisone (CbP) or cyclophosphamide/vincristine (Oncovin)/prednisone (COP). Patients underwent treatment only when their disease status was considered to require therapeutic intervention, as defined by the presence of systemic B symptoms, haematopoietic insufficiency, progressive lymphoma or bulky disease.

The study protocol is shown in Figure 1. Initial cytoreductive chemotherapy consisted of the combination of prednimustine 100 mg/m²/day given orally days 1-5, and mitoxantrone 8 mg/m²/day as a 30-min intravenous infusion delivered on days 1 and 2. In the event of post-therapeutic neutropenia

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(<1,000 cells/mm³) or thrombocytopenia (<75,000 cells/mm³), subsequent cycles were given at a lower dose with prednimustine 100 mg/m²/day being applied only on days 1-4, and mitoxantrone being reduced to one 30-min infusion of 12 mg/m² on day 1. The prednimustine and mitoxantrone (PmM) regimen was repeated every 4 to 6 weeks to a maximum of six cycles. Patients achieving complete or partial remissions (CR or PR) received two additional cycles for consolidation followed by interferon alfa-2b 5 million units (MU) subcutaneously (s.c.) three times weekly (t.i.w.) until progression or relapse [12].

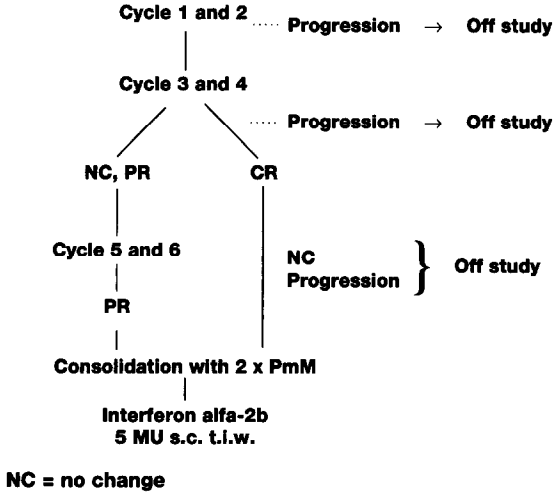

Fig. 1. Schematic diagram of the PmM/Interferon alfa-2b pilot study protocol.

Prior to PmM therapy, the extent of the disease was documented by chest radiography, abdominal sonography, bone marrow biopsy, and computerized tomography of the chest and/or abdomen. The relevant diagnostic procedures were repeated after every two cycles of treatment to assess the therapeutic response. CR was defined as the elimination of all measurable disease for at least 4 weeks and a normalization of peripheral blood counts. PR was defined as a reduction of disease manifestations by at least 50% for more than 4 weeks. Treatment-related toxicity was evaluated according to World Health Organization (WHO) criteria.

RESULTS

The 19 patients entered into the PmM/interferon pilot study were aged 33 to 74 years (median 59 years). Histological subtypes according to the Kiel classification included 13 centroblastic-centrocytic lymphomas, three centrocytic lymphomas, and three lymphoplasmacytoid immunocytomas. All patients had received previous therapy with CbP and/or COP. In five cases, additional radiotherapy had been applied.

All patients received at least two PmM courses. A total of 137 treatment cycles have been administered so far, with a median of five courses per patients. Four of the 19 patients achieved CR and in a further nine patients PR was obtained, resulting in an overall response rate of 68% (13/19). In two cases, disease manifestations remained unchanged, while progressive disease was diagnosed in four patients. Response to the PmM regimen was already apparent after two cycles, by which time all 13 responding cases showed a reduction in the lymphoma cell mass of at least 50%.

Side effects consisted predominantly of myelosuppression and leukocytopenia, requiring dose reduction in 48% of treatment courses.

All 13 responding patients received interferon alfa-2b maintenance treatment as outlined above. Dose reductions were necessary in 30% of cases, mainly because of haematological toxicity. At present, remission duration ranges from 4.5+ to 17.5+ months (median 14.5 months). In a historical comparison to unmaintained first remissions preceding the PmM/interferon trial, a clear tendency towards a longer period of freedom from progression emerged with the interferon alfa-2b maintenance treatment during a second PR or CR (Figure 2).

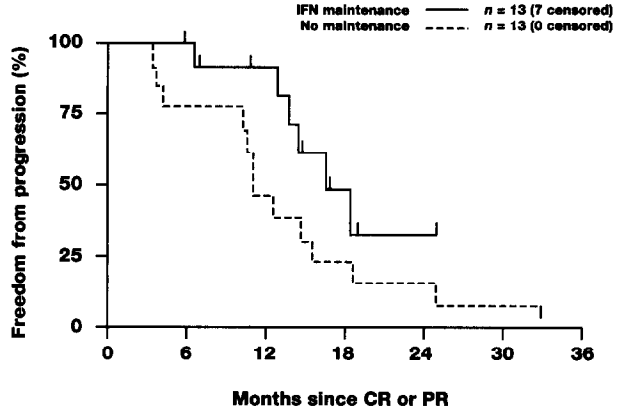

Fig. 2. Freedom from progression curves for patients receiving the PmM salvage followed by interferon alfa-2b in second CR or PR (solid line) in comparison to first-line chemotherapy without interferon (broken line).

DISCUSSION

The present study confirms the recently reported high anti-lymphoma activity of the PmM combination [11], although a higher degree of toxicity, in particular myelosuppression, was observed, requiring dose reduction in 48% of treatment cycles. In addition, preliminary evidence suggests that subsequent maintenance therapy with interferon alfa-2b may prolong progression-free interval. The dose of interferon alfa-2b was adjusted according to experience of side effects, which consisted mainly of myelotoxicity. Only two patients required discontinuation of treatment, while the remaining 11 cases either are still on treatment or tolerated interferon therapy until clinical progression.

These encouraging results are based on small numbers of patients and deserve confirmation with a larger accrual of cases and longer observation times. In addition, data must be compared with those for standard therapeutic modalities and must be judged according to the ultimate goal of prolonged survival. Hence, a multicentre trial was initiated in newly diagnosed advanced low-grade NHL, randomly comparing PmM versus COP for initial cytostatic treatment [13]. So far, a total of 132 patients have been enrolled into this ongoing study, 77 of whom are currently evaluable for response and toxicity. Overall, CR was achieved in 34 cases (44%) while an additional 29 patients (38%) obtained a PR. Side effects were mild to

moderate, with neutropenia occurring in 33% of treatment courses only. Further accrual of patients and longer observation times are needed to confirm these promising results and to disclose the comparative analysis of PmM versus COP and interferon maintenance versus observation only.

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Role of Interferon Alfa-2b in the Management of Patients with Advanced Cutaneous T-Cell Lymphoma

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INTRODUCTION

CUTANEOUS T-cell lymphomas (CTCL) are a group of rare disorders comprising primarily mycosis fungoides and Sezary's syndrome. Characteristically, CTCL commences with skin lesions and subsequent systemic spread. Prognosis is related to type of skin lesions and presence or absence of systemic involvement. In general, they are fairly indolent, with a median survival approaching 10 years.

Until recently, no therapeutic modality has shown any substantial benefit. Conventional treatment has been with a variety of alkylating agents, steroids, electron beam therapy and PUVA therapy, resulting in a modest, usually short-lived benefit.

PREVIOUS STUDIES

In 1983, Bunn and colleagues [1] investigated the role of alpha interferon at high doses (50 million units [MU]/m^2 three times a week [t.i.w.]) and observed an objective response rate of 45%. Several subsequent trials [2-5] utilizing relatively lower doses of alpha interferon (3-10 MU) have since been completed and overall responses of 58% observed. These responses have been noted in patients with both cutaneous and extracutaneous manifestations and in both previously treated and previously untreated groups.

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PRESENT STUDY

Patients and methods

We have treated three patients with advanced, previously untreated CTCL. All patients received interferon alfa-2b 5 MU t.i.w. subcutaneously for 90 days, followed by a progressive dose escalation in responders to a maximum of 20 MU t.i.w.

Results

One of the three patients developed progressive disease and was taken off interferon after 30 days. The other two patients demonstrated a partial remission after 90 days of interferon therapy. The dose was then escalated to 20 MU t.i.w. Both patients went on to achieve a complete remission (CR) at 4 months from initiation of interferon. One of these two patients