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Lymphoma

High-dose therapy and autologous stem cell transplantation in relapsing cutaneous lymphoma

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Summary:

Treatment of cutaneous T-cell and B-cell lymphomas is difficult and relapses are frequent. To evaluate the efficiency of high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) on relapsing cutaneous lymphomas, we conducted a retrospective study of 14 patients. We investigated the clinical and histological parameters of the lymphoma, previous treatments to ASCT, short-term complications of ASCT, and occurrence of a relapse. There were 11 males and three females, with a median age of 42 years. Most often, the skin disease was disseminated without extracutaneous involvement. Four patients had a B-cell lymphoma and 10 a T-cell lymphoma. CD30 was negative in 8/10 T-cell lymphomas. Before ASCT, 13 patients had chemosensitive disease; one had refractory disease. The conditioning regimen included TBI in nine cases. No toxic death occurred. Relapse of the lymphoma occurred in eight cases (T-cell lymphoma in seven cases), within 4 months after ASCT in six cases. Relapses were treated with local treatment, interferon or classical chemotherapy. At the end of the study, 11 patients were alive and three patients had died. HDT and ASCT do not benefit patients with T-cell lymphomas. For patients with disseminated relapsing cutaneous B-cell lymphomas, this procedure should be considered.

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Primary cutaneous lymphomas represent the second most common subgroup of extranodal lymphomas after those involving the gastrointestinal tract.[1,2] They include T-cell epidermotropic or nonepidermotropic lymphomas and B-cell lymphomas, according to histological classifications.[1,3] More than 70% of patients present with disease limited to the skin, while the remaining patients show extracutaneous localization, involving lymph-node and/or bone marrow in most cases.[4] Therapeutic indications depend both on the histological subtype and on the staging of the disease. Thus, while early stages of mycosis fungoides (MF), the most frequent form of epidermotropic cutaneous T-cell lymphoma (CTCL), require topical chemotherapy or PUVA therapy, systemic immunomodulatory treatment with alpha interferon and/or antineoplastic polychemotherapy are indicated in advanced stages, although these latter treatments usually provide transient and incomplete responses.[5] While localized forms of primary cutaneous B-cell lymphomas and nonepidermotropic T-cell lymphoma usually respond to radiotherapy, single-agent antineoplastic chemotherapy or polychemotherapy are needed in disseminated stages, but relapses are frequently observed.[6,7] Indeed, disseminated forms of large-cell lymphoma primarily involving the skin are associated with a poor prognosis, as illustrated by the estimated survival of 40% in patients affected with disseminated forms of CD30-negative, large T-cell lymphomas.[6,8] Taking these data into account, innovative therapies are warranted in patients with high-grade cutaneous lymphoma, especially those exhibiting high tumor burden.

Recently, high-dose therapy (HDT) followed by autologous stem-cell transplantation (ASCT) have been associated with an increase in disease-free survival in aggressive lymphomas showing resistance or relapse after antineoplastic multiple drug therapy.[9,10] Moreover, ASCT has also been applied to cases of low-grade lymphomas showing relapse after conventional therapy, with promising results.[11,12,13]

We report here the results from a retrospective study in 14 patients with T- or B-cell cutaneous lymphomas showing replapse after polychemotherapy.

Patients and methods

Patients

We retrospectively reviewed the files of 14 patients with relapsing T-cell or B-cell cutaneous lymphoma, who

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underwent HDT and ASCT between 1987 and 2001. Patients were initially seen in one of two Departments of Dermatology in Saint-Louis Hospital, and were then referred to the Department of Onco-Hematology of the same hospital to undergo ASCT.

For each patient, we investigated the following clinical parameters: sex, age at the time of the ASCT, performance status (PS), organs involved at presentation, clinical type of skin lesions (plaques, papules, nodules), and extent of cutaneous involvement (localized disease covering less than 10% of the tegument or disseminated disease covering more than 10%).

The initial staging included biological tests with lactate-dehydrogenase (LDH) blood level expressed as abnormal when above the normal range, thoracoabdominal computerized X-ray scan, and bone marrow biopsy.

All treatments given prior ASCT were noted: localized treatments such as PUVA therapy, chlormethine or external localized radiotherapy, and systemic antineoplastic chemotherapies. Disease status of the patient at the time of the ASCT was analyzed according to standard criteria for lymphomas,[14] and patients were considered as having a chemosensitive disease when they had achieved a complete or partial response $>50\%$ after chemotherapy, while the remaining patients were considered to have refractory disease. We investigated the short-term complications of the ASCT and the occurrence of relapse. The interval between ASCT and relapse, disease localization at the time of relapse, its histological subtype, and the treatment were specified. The disease status of patients at the end of study (January 2003) was also evaluated.

Histology

Cutaneous histological sections of the initial and the relapsing lesions were reviewed by one expert in the field of oncological dermatopathology (OV). Biopsy specimens were classified according to the EORTC and the REAL classifications of primary cutaneous lymphomas.[1,3] Immunohistochemical analysis was performed in all cases either on frozen biopsies or on paraffin sections stained with anti-CD2, CD3, CD4, CD8, CD5, CD7, CD30, CD19, and CD20 monoclonal antibodies (MAb). Molecular analysis of clonality was performed in 11 cases using multiplex polymerase chain reaction-based amplification of Vγ-Jγ and VH-JH DNA rearrangements.

High-dose therapy

Peripheral blood progenitor cells (PBPC) were collected from two to three leukaphereses during hematological recovery following mobilizing chemotherapy plus G-CSF, and bone marrow was harvested under general anesthesia and further cryopreserved, as previously described.[15]

The conditioning regimen included either a high-dose polychemotherapy alone or in combination with total body irradiation (TBI, 12 Gy in six fractions over 3 days) when it was technically possible and when the patient had not previously received radiotherapy. TBI was delivered through a 12 Mev linear accelerator at 5 cGy/mn, with lung shielding at 8 Gy.

Results

Characteristics of patients (Table 1)

There were 11 males and three females with a median age of 42 years (9–58 years). All patients had a PS <2 without major organ failure, except two patients who had controlled coronary ischemic disease. Skin involvement was the first manifestation of the disease in all patients, even in patient 1 who had a diagnosis of Hodgkin's disease on lymph-node biopsy.

In all, 11 patients presented with disseminated skin disease (erythematous and squamous plaques, nodules), while three patients had a localized form consisting in one or two lesions. A total of 10 patients were free of extracutaneous involvement at initial staging.

At the initial phase of their disease, three patients presented with a superficial lymphadenopathy, one had bone marrow involvement, one patient had abnormal cells showing cytonuclear abnormalities on cytological analysis of peripheral blood and bone marrow samples (case 7), and, finally, one patient showed splenic involvement (case 14). LDH serum levels were within the normal range in 11 of 13 patients.

Histological and immunostaining studies (Table 2)

Four patients had a cutaneous lymphoma of B lymphocytic lineage: one with cutaneous localization of Hodgkins disease, one with follicle center-cell lymphoma, and two with diffuse large-cell lymphoma.

A total of 10 patients had CTCL. One patient had MF, one patient was diagnosed with subcutaneous panniculitis-like T-cell lymphoma, three patients had pleomorphic small-/medium-sized cell lymphoma, and pleomorphic large T-cell lymphoma was diagnosed in the five remaining cases. Immunostaining with anti-CD4 and CD8 Mab showed that T-cell lymphomas were CD4+ in nine cases, and CD8+ in one case. Immunostaining with anti-CD30 Mab showed immunoreactivity of tumor cells in two pleomorphic large T-cell lymphomas and yielded negative results in the remaining cases.

Results from PCR-based analysis of the clonality status of tumor lesions revealed the presence of a predominant rearrangement of the IgH locus in 2/4 B-cell lymphomas, while a clonal rearrangement of Vγ genes was detected in lesions from 5/7 cases of T-cell lymphomas.

Previous treatments

All patients had received therapies prior to the onset of ASCT: five patients who initially received PUVA therapy ($n=1$), chlormethine ($n=2$), and/or external localized radiotherapy at 30 Gy ($n=2$) were treated with polychemotherapy as second-line regimen. The nine other patients received 1, 2 or 3 lines of polychemotherapy (median at 2), including anthracyclines and/or cisplatinum (Table 1).

ASCT

Before HDT and ASCT, one patient (case 6) had a progressive and refractory disease with persistence of

Table 1 Characteristics of patients pre-ASCT

Patient	*Sex M/F*	*Age*	*Date of diagnosis*	*Initial extracutaneous involvement LN/BM*	*Type of lesions; localized (L) or disseminated (D)*	*LDH*	*Treatments prior ASCT*	*Interval between diagnosis and HDT (months)*
1	M	45	1990	+/−	Nodules; D	N	ABVPP; CEOP	33
2	M	37	1998	−/−	Papules and nodules; D	N	CHOP; DHAP	15
3	F	52	1998	−/−	Nodules; L	N	CEOP-RXth; CHOP	27
4	M	29	1991	−/−	Nodules; D	N	Chloraminophen; mini-CHVP; CHOP	36
5	M	58	1994	−/−	Plaques; L	?	CHOP; ESHAP	44
6	M	33	1988	−/−	Granulomatous chalazoderma; D	N	Chlormethine; CHOP-ESHAP	96
7	M	56	1991	−/+; Blood	Plaques; D	1.5N	CHOP + Rxth; CyclophosphamideIVAM	13
8	F	38	1989	−/−	Nodule; L	N	RXth; ACVBP; DHAP-CHOP	38
9	M	36	1986	−/−	Plaques, nodules; D	N	CHOP; MTX-prednisone; IFN; IVAM; MAMIE	19
10	M	29	1988	−/−	Nodules; D	N	RXth; chloraminophen; ACVBP; IVAM	40
11	M	51	1989	−/−	Plaques; D	N	CHOP; electron; IVAM	9
12	M	57	1997	−/−	Plaques; D	1.5N	Chlormethine; ACVBP	22
13	M	55	1990	+/−	Plaques; D	N	PUVA; IFN-pUVA; ESHAP	127
14	F	9	1993	+/−; Spleen	Plaques; D	N	ACVBP, MTX, vinblastine; bleomycin	7

M = male; F = female; LN = lymph node; BM = bone marrow; LDH = lactate dehydrogenase; HDT = high-dose therapy; ABVPP = adriamycin, bleomycin ,vinblastine, procarbazine, and prednisone; CEOP = cyclophosphamide, epirubicin, vincristine, and prednisone; CHOP = adriamycin, cyclophosphamide, vincristine, and prednisone; DHAP = dexamethasone, aracytine, and cisplatine; mini-CHVP = low-dose adriamycin, cyclophosphamide, VP16, and prednisone; ESHAP = etoposide, methylprednisolone, aracytine, and cisplatine; ACVBP = adriamycin, cyclophosphamide, vindesin, bleomycin, and prednisone; MTX = methotrexate; IFN = alpha-interferon; IVAM = ifosfamide,VP16, aracytine, and methotrexate; MAMIE = ifosfamide, mitoxantrone, méthylgag, VM26; Rxth = radiation therapy.

multiple lesions and 13 patients had sensitive disease (92% were in CR). The median time between diagnosis of lymphoma and ASCT was 38 months (7–127). In nine cases, conditioning regimens included TBI that was associated with high-dose chemotherapy (VP16, cyclophosphamide, aracytine, and/or melphalan). The five other patients received the BEAM regimen (BCNU, etoposide, aracytine, and melphalan).[16]

In all, 13 patients received a PBPC transplantation and one patient received a bone marrow transplant. After HDT, all patients retained normal blood counts within the normal range,[15] with a median duration of neutropenia $<0.5\times10^9$/l of 12 days. However, one patient presented with delayed engraftment, requiring hematopoietic growth factor treatment for several weeks.

A total of 11 patients had prolonged fever, which remained of unknown origin in nine cases, and was related to *Staphylococcus epidermidis* septicaemia in two cases. One patient (case 6) with pulmonary infection required intensive care and mechanical ventilation, while patient 1 had reactivation of a B virus hepatitis 3 months after the HDT and developed a hepatic fibrosis. No death occurred during the procedure.

Disease status and response

Following HDT, eight patients (T-cell lymphoma in seven cases) relapsed. Six of these patients relapsed within 4 months following the HDT, and one patient relapsed 7 years after ASCT. Patient 8, who had a follicle center cell lymphoma, relapsed 5 years after ASCT. Histological classification of relapsing lesions, treatment of the relapse, and the present disease status of the patients are detailed in Table 3. Four relapsing patients are now in CR for the cutaneous disease, with a follow-up of 3–7 years. CR was obtained with local therapies, interferon or standard polychemotherapies, and one patient received interleukin 2 (case 11).[17] At the end of the study (January 2003), two other patients retain cutaneous disease: one is in partial remission (case 8) and one has a progressive disease (patient 13). Three patients experienced a fatal progression (24%): one patient died of early relapse involving the central nervous system (case 7), and patient 12 died 2.5 years after ASCT due to progressive cutaneous disease, showing resistance to three different antineoplastic multiple agent antineoplastic drug therapy. Finally, death in case 5 was related to bone marrow failure with progressive disease.

Four patients did not show evidence of relapse during follow-up: one patient with Hodgkin disease (case1, six years follow-up), two patients with diffuse large-cell B lymphoma (case 2 after 36 months of follow-up and case 3 during 15 months of follow-up), and one patient with pleomorphic small—medium-sized T-cell lymphoma (case 10, 9 years follow-up).

Discussion

ASCT has been increasingly used for the treatment of relapsing and refractory lymphomas. The disease-free survival rates vary from 30 to 50%, mostly depending on

Table 2 Histological classification

Patient	*EORTC classification*	*REAL classification*	*Cutaneous clone*
1	Cutaneous localization of a Hodgkin disease (EORTC and REAL not listed)		Minor B-cell clone
2	Not listed	Diffuse large B-cell lymphoma	Negative
3	Not listed	Diffuse large B-cell lymphoma	Minor B-cell clone
4	Follicle center cell lymphoma	Follicle center lymphoma, mixed small and large cell	Negative
5	Pleomorphic small-/medium sized cell	Peripheral T-cell lymphoma, unspecified	Negative
6	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitic T-cell lymphoma	T-cell clone
7	CD30-positive large T-cell lymphoma pleomorphic	Peripheral T-cell lymphoma, unspecified	Negative
8	CD30-negative large T-cell lymphoma pleomorphic	Peripheral T-cell lymphoma, unspecified	T-cell clone
9	CD30-negative large T-cell lymphoma pleomorphic	Peripheral T-cell lymphoma, unspecified	ND
10	Pleomorphic small-/medium-sized cell	Peripheral T-cell lymphoma, unspecified	ND
11	MF	MF	ND
12	CD30-negative large T-cell lymphoma pleomorphic	Peripheral T-cell lymphoma, unspecified	Minor T-cell clone
13	CD30-positive large T-cell lymphoma pleomorphic	Peripheral T-cell lymphoma, unspecified	Massive T-cell clone
14	Pleomorphic small-/medium-sized cell lymphoma	Peripheral T-cell lymphoma, unspecified	Massive T-cell clone

MF = mycosis fungoides; ND = not done.

the response of the disease to antineoplastic chemotherapy.[9,10] The toxicity and secondary morbidity of HDT decreased in recent years with the use of hematopoietic growth factors and PBPC, compared to bone marrow transplantation.[15] We report here the results from HDT and ASCT in 14 young patients with relapsing cutaneous lymphoma of various histological subtypes (10 T-cell and four B-cell lymphomas). HDT was offered to a very small number of patients, only to patients with aggressive, relapsing, but chemosensitive disease (12 of our patients were in CR at the HDT time). First, this situation is rare regarding the total number of patients with cutaneous lymphomas treated in our hospital in the same period: actually, nonepidermotropic aggressive but chemosensitive T-cell lymphomas are much less frequent than epidermotropic T-cell lymphomas such as MF. Second, this situation is rare compared to the total number of lymphomas of any type or localization receiving HDT and ASCT (about 30–40 patients receive ASCT each year in our hospital). The procedure was most often well tolerated, but, in our experience, even if histologies were heterogeneous, HDT showed no efficacy in most patients with CTCL, since 60% of these patients experienced an early relapse (median time duration from ASCT to relapse: 4 months). These poor results may, in part, be supported by the observation that the T-cell phenotype was shown to be an independent poor prognosis significant factor in aggressive non-Hodgkin's lymphomas.[18] Concerning the four patients with B-cell lymphoma, one of them with a disseminated disease relapsed locally 5 years after ASCT, and three were in CR. Thus, it is likely that relapsing cases of cutaneous B-cell lymphomas are a good target of HDT and ASCT, a notion also supported by reports in patients with nodal B-cell lymphomas.[19] Indeed, with the use of hematopoietic growth factors and mobilized PBPC, TBI combined with high-dose chemotherapy is feasible, is associated with limited toxicity, and delivers treatment to the entire skin. TBI was used in the first reports of ASCT for the treatment of advanced lymphomas, in conjunction with high-dose chemotherapy (cyclophosphamide with or without etoposide).[13] In our study, it was not always possible to include TBI in the conditioning regimen because of technical reasons or when the patient had previously received radiotherapy. We also observed late relapses despite the use of TBI, indicating that this latter regimen does not necessarily cure skin disease, but may contribute to the control of the disease. In view of our results, radiation therapy delivering higher dosages to the skin is warranted for the treatment B-cell non-Hodgkin's lymphomas.

Five previously published studies investigated HDT and ASCT in patients with cutaneous lymphomas. Bigler *et al*[20] reported six patients with MF who underwent ASCT after a conditioning regimen that included TBI or total skin electron beam radiotherapy. Five patients were in CR after the HDT, but three patients relapsed within 100 days. Two patients were in persistent CR 1 year after the procedure. We concluded that this procedure is feasible and safe in patients with MF, despite a limited follow-up. In another study, Moreau *et al*[21] reported four patients, two with a B-cell lymphoma, two with a CD30+ T-cell lymphoma who received a conditioning regimen including TBI, and who where in CR after a mean follow-up of 45 months. More recently, Fanin *et al*[22] reported a larger series of 16 patients with CD30+ cutaneous lymphoma, eight with a B-cell lymphoma, four with CTCL, and four with a lymphoma bearing a null phenotype. The patients underwent ASCT without using TBI. All patients achieved a persistent CR following autologous bone marrow transplantation, during a median follow-up of 33.5 months. In this latter series, the beneficial results might be explained by the fact that tumor cells were CD30+, which is known to be a factor of favorable prognosis, in contrast with our series, which mostly gathered CD30− CTCLs. Olavarria *et al*[23] reported a series of nine patients with tumor stage MF, of whom eight had also a circulating T-cell clone in the peripheral blood. The conditioning regimen involved TBI in two cases. One patient died from septicemia during the neutropenia period. Seven patients relapsed at a median of 7 months after the graft, most with less aggressive disease, which responded to conventional therapy. The authors concluded that ASCT is feasible, safe, and that, despite the high rate of recurrence, control of relapsing disease was satisfactory. Two other patients with advanced MF were treated unsuccessfully with HDT, TBI, and ASCT, relapsing less than 3 months after the procedure.[24,25]

Table 3 Characteristics of relapsing cases

Patient	*Initial histology*	*Conditioning regimen*	*Delay between the graft and the relapse (months)*	*Localization and histology of the relapse after the graft*	*Treatment of the relapse*	*Present status in 01/2003 (median follow-up (months))*
4	Follicle center cell lymphoma	TBI, etoposide, cyclophosphamide	60	Two cutaneous nodules; follicle center cell lymphoma	Localized RXth	CCR (42)
7	CD30-positive large T-cell lymphoma pleomorphic	BEAM	1	Skin and brain; nonbiopsy	Cerebral RXth	Dead
8	CD30-negative large T-cell lymphoma pleomorphic	TBI, etoposide, cyclophosphamide	84	Skin; CD30 positive large T-cell lymphoma pleomorphic	CEOP, IFN, chlormethine	PR (48)
9	CD30-negative large T-cell lymphoma pleomorphic	Etoposide, cyclophosphamide melphalan	<1	Skin; no biopsy	Chloraminophen RXth; IFN	CCR (96)
11	MF	BEAM	2.5	Skin; MF then CD30-positive large T-cell lymphoma	IL2; PCOP, etoposide	CCR (84)
12	CD30-negative large T-cell lymphoma pleomorphic	TBI, cyclophosphamide	4	Skin; MF	Chlormethine, pUVA therapy, IFN; PCOP; DHAP; GEMOX	Dead
13	CD30-positive large T-cell lymphoma pleomorphic	BEAM	3	Skin; CD30 positive large T-cell lymphoma pleomorphic	Arsenic trioxide; bexaroten; PACOP	Progressive disease
14	Pleomorphic small-/medium-sized cell lymphoma	TBI, aracytine, melphalan	1	Skin; no biopsy	IFN	CCR (96)

CCR = continuous complete remission; TBI = total body irradiation; BEAM = BCNU, etoposide, aracytine, melphalan; IFN = interferon; RXth = radiotherapy; CEOP = cyclophosphamide, epirubicin, vincristine, and prednisone; DHAP = dexamethasone, aracytine, and cisplatine; IL2 = interleukin-2; PACOP = procarbazine, adriamycine, cyclophosphamide, vincristine, prednisone; GEMOX = gemcitabine, oxaliplatine.

In view of the results presented here, despite the retrospective nature of our series and concerns about heterogeneous histologies, we postulate that HDT followed by ASCT is unlikely to offer significant benefit to most patients with CTCL, while results observed in patients with cutaneous B-cell lymphomas suggest that HDT and ASCT may be considered as an alternative treatment for young patients with relapsing, disseminated lesions, with the same prognostic factors as lymph-node lymphomas. Prospective studies, however, investigating ASCT of larger series of patients with homogenous histologies, especially in the case of cutaneous B-cell lymphomas, are warranted to accurately evaluate the benefits of this procedure.

References

1 Sander CA, Kind P, Kaudewitz P *et al*. The REAL classification of lymphoid neoplasms: a new perspective for the classification of cutaneous lymphoma. *J Cutan Pathol* 1997; **24**: 329–341.
2 Mirza I, Macpherson N, Paproski S *et al*. Primary cutaneous follicular lymphoma: an assessment of clinical, histopathologic, immunophenotypic and molecular features. *J Clin Oncol* 2002; **20**: 647–655.
3 Willemze R, Kerl H, Sterry W *et al*. EORTC classification for primary cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the European organization for research and treatment of cancer. *Blood* 1997; **1**: 354–371.
4 Knobler RM, Edelson RL. Cutaneous T cell lymphoma. *Med Clin North Am* 1986; **70**: 109–138.
5 Kaye FJ, Bunn PA, Steinberg SM *et al*. A randomised trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *New Engl J Med* 1989; **321**: 1784–1790.
6 Burke JS, Hoppe RT, Cibull ML, Dorfman RF. Cutaneous malignant lymphoma, a pathologic study of 50 cases with clinical analysis of 37. *Cancer* 1981; **47**: 300–310.
7 Brice P, Cazals D, Mounier N *et al*. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. *Leukemia* 1998; **12**: 213–219.
8 Joly P, Charlotte F, Leibowitch M *et al*. Cutaneous lymphomas other than mycosis fungoides: follow up study of 52 patients. *J Clin Oncol* 1991; **9**: 1994–2001.
9 Bosly A, Coiffier B, Gisselbrecht C *et al*. Bone marrow transplantation prolongs survival after relapse in aggressive lymphoma patients treated with the LNH84 regimen. *J Clin Oncol* 1992; **10**: 1612–1623.
10 Philip T, Guglielmi C, Hagenbeek A *et al*. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; **333**: 1540–1545.
11 Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphoma. *Semin Oncol* 1993; **20** (Suppl. 5): 75–88.
12 Freedman AS, Ritz J, Neuberg D *et al*. Autologous bone marrow transplantation in 69 patients with a history of low-grade B-cell non Hodgkin's lymphoma. *Blood* 1991; **77**: 2524–2529.
13 Bastion Y, Brice P, Haioun C *et al*. Intensive therapy with peripheral blood progenitor cell transplantation in 60 patients with poor-prognosis follicular lymphoma. *Blood* 1995; **86**: 3257–3262.
14 Cheson BD, Horning SJ, Coiffier B *et al*. Report of an international workshop to standardize response criteria for

non-Hodgkin's lymphomas. NCI sponsored international working group. *J Clin Oncol* 1999; **17**: 1244.
15 Brice P, Marolleau JP, Pautier P *et al*. Hematologic recovery and survival of lymphoma patients after autologous stem-cell transplantation: comparison of bone marrow and peripheral blood progenitor cells. *Leuk Lymphoma* 1996; **22**: 449–456.
16 Gribben JG, Linch DC, Singer CR *et al*. Successful treatment of refractory Hodgkin's disease by high-dose combination chemotherapy and autologous bone marrow transplantation. *Blood* 1989; **73**: 340–344.
17 Marolleau JP, Baccard M, Flageul B *et al*. High dose recombinant interleukin-2 in advanced cutaneous T-cell lymphoma. *Arch Dermatol* 1995; **131**: 574–579.
18 Gisselbrecht C, Gaulard P, Lepage E *et al*. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. *Blood* 1998; **92**: 76–82.
19 Shipp MA. Prognostic factors in aggressive non-Hodgkin's lymphoma: who has 'high-risk' disease? *Blood* 1994; **83**: 1165–1173.
20 Bigler RD, Crilley P, Micaily B *et al*. Autologous bone marrow transplantation for advanced stage mycosis fungoides. *Bone Marrow Transplant* 1991; **7**: 133–137.
21 Moreau P, LeTortorec S, Mahé MA *et al*. Autologous bone marrow transplantation using TBI and CBV for disseminated high/intermediate grade cutaneous non-epidermotropic non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1994; **14**: 775–778.
22 Fanin R, Silvestri F, Geromin A *et al*. Primary systemic CD30 (Ki-1)-positive anaplastic large cell lymphoma of the adult: sequential intensive treatment with the F-MACHOP regimen (+/−radiotherapy) and autologous bone marrow transplantation. *Blood* 1996; **4**: 1243–1248.
23 Olavarria E, Child F, Woolford A *et al*. T-cell depletion and autologous stem cell transplantation in the management of tumour stage mycosis fungoides with peripheral blood involvement. *Br J Haematol* 2001; **114**: 624–631.
24 Sterling JC, Marcus R, Burrows NP, Roberts SOB. Erythrodermic mycosis fungoides treated with total body irradiation and autologous bone marrow transplantation. *Clin Exp Dermatol* 1995; **20**: 73–75.
25 Ferra C, Servitje O, Petriz L *et al*. Autologous haematopoietic progenitor transplantation in advanced mycosis fungoides. *Br J Dermatol* 1999; **140**: 1188–1189.