Multiple biopsies revealed chronic lymphoadenitis and lymphoepithelial thymoma. After mediastinal radiotherapy the patient was well until January 1996, when fever reappeared together with hepatosplenomegaly and a generalized edematous state. Splenectomy revealed a fibrocongested spleen, abdominal lymph nodes had abundant plasma cells, a liver biopsy was normal. She was treated with antibiotics and steroids, but the fever returned when the prednisone dose was tapered down.

She was referred to our clinic in December 1996, with sustained fever, lymphoadenopathy, and hepatomegaly. Lymph node biopsy established the diagnosis of plasma cell-rich MCD. Physical examination also revealed small, raised, reddish-purple cutaneous nodules on the right knee and both ankles, which had appeared two years before. Histology confirmed the clinical suspicion of KS. Visceral KS localizations were detected on the hard palate and in the stomach. Serum IL-6 levels were extremely high (1,850 pg/mL); serum anti-HHV8 antibodies were present and plasma HHV8 positivity was confirmed by PCR.

The rapid clinical deterioration, irrespective of steroids, prompted us to add a single dose of intravenous (iv) cyclophosphamide (30 mg/kg). An evident clinical and laboratory improvement was complicated by disseminated intravascular coagulation and cerebral hemorrhage. One month later hematologic and neurologic problems were stable; a relapse of MCD led us to restart cyclophosphamide with an iv pulse (25 mg/kg) followed by oral administration (2 mg/kg/die) together with prednisone (1 mg/kg/die). The fever disappeared and the enlarged lymph nodes shrank. Erythrocyte sedimentation rate, C-reactive protein, and liver function all improved; IL-6 dropped to levels seen in normal control subjects (164.6±119.3 pg/mL). Steroids were tapered down to 10 mg/day.

In May 1997 a cutaneous spreading of KS required local radiotherapy. α-interferon was tried briefly, but was stopped because of severe depression. Considering the possibility that the impressive polyclonal plasma cell differentiation of MCD might be under the control of the T-cell system and that the T-cell immunoregulatory circuits might also be abnormal,[4] we added cyclosporin A (CyA 4 mg/kg/die) to oral cyclophosphamide. The palpable lymph nodes did not increase in size and no new nodes appeared. Unexpectedly, we also observed beneficial effects on the KS lesions. Skin and hard palate nodules progressively reduced in size and some disappeared. No new lesions could be detected in the skin or in the stomach. In April 1998, because of the high cumulative dose, cyclophosphamide was interrupted, while CyA was continued at an unvaried dosage. Since then the patient's clinical, radiological and laboratory findings have been stable suggesting that cyclophosphamide and low dose CyA may be used to achieve a satisfactory and prolonged control of both lymphoid and KS cell proliferation in MCD.

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References

1. Peterson BA, Frizzera G. Multicentric Castleman's disease. Semin Oncol 1993; 20:636-47.
2. McCarty MJ, Vukelja SJ, Banks PM, Weiss RB. Angiofollicular lymph node hyperplasia (Castleman's disease). Cancer Treat Rev 1995; 21:291-310.
3. Bowne WB, Lewis JJ, Filippa DA, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 1999; 85:706-17.
4. Ohyashiki JH, Ohyashiki K, Kawakubo K, et al. Molecular genetic, cytogenetic, and immunophenotypic analyses in Castleman's disease of the plasma cell type. Am J Clin Pathol 1994; 101:290-5.

High-dose ifosfamide and etoposide infusion plus methylprednisolone for refractory or relapsed aggressive non-Hodgkin's lymphoma

The prognosis of patients with aggressive non-Hodgkin's lymphoma (NHL) who fail to achieve a complete remission with first-line anthracycline-containing chemotherapy or who relapse remains poor.[1–4] Many salvage regimens have been reported for these patients with varying effectiveness and very poor chance of long-term survival.[1,2] Ifosfamide has been included in some of these regimens, often in association with etoposide.[1,2,5,6] Improved survival may be obtained with high dose chemotherapy and autologous hematopoietic stem cell transplantation, especially in chemosensitive relapses.[7,8]

Sir,

We designed a novel salvage program including high-dose ifosfamide infusion plus high-dose fractionated etoposide and methylprednisolone (IFOVM), followed by DHAP chemotherapy[9] and subsequent intensive chemotherapy with autologous peripheral blood stem cell transplantation (APBSCT) for patients with refractory or relapsed aggressive NHL.

Between November 1996 and December 1998, 20 consecutive patients were included in this protocol. Patient characteristics at diagnosis are summarized in Table 1. Informed consent was obtained from all patients.

IFOVM induction salvage chemotherapy consisted of ifosfamide (10 g/m^2 as a 72-hour continuous intravenous infusion on days 1-3), etoposide (150 mg/m^2 every 12 hours as a 2-hour i.v. infusion on days 1 to 3), mesnum (20% of the total dose of ifos-

Table 1. Patient characteristics at diagnosis and during progression prior to IFOVM.

	At diagnosis N (%)	*During progression N (%)*
Stage		
I-II	3 (15)	5 (25)
III-IV	17 (85)	15 (75)
B symptoms		
No	9 (45)	7 (35)
Yes	11 (45)	13 (65)
LDH		
≤ 1 n. v.	6 (30)	9 (45)
> 1 n. v.	14 (70)	11 (55)
β_2-microglobulin		
≤ 1 n. v.	6 (30)	16 (80)
> 1 n. v.	11 (55)	4 (20)
Not done	3 (15)	
Performance status		
0-1	9 (45)	11 (55)
2-4	11 (55)	9 (45)
IPI		
0	2 (10)	1 (5)
1-2	4 (20)	12 (60)
3-4	13 (65)	6 (30)
5	1 (5)	1 (5)
Tumor score		
0	2 (10)	0
1-2	5 (25)	11 (55)
3-4	8 (40)	6 (30)
5	5 (25)	3 (15)
Histology		
DLBCL		17 (85)
PTCL		3 (15)
No. of prior chemotherapies		
1		12 (60)
2		7 (35)
≥ 3		1 (5)
Type of chemotherapy		
CHOP		17 (85)
MegaCHOP		1 (5)
MACOP-B		1 (5)
Others		1 (5)
Prior radiotherapy		
No		16 (80)
Yes		4 (20)
Previous response to therapy		
Primary refractory		9 (45)
Acquired refractory		5 (25)
Relapsed		6 (30)
Time from last treatment		
≤ 6 months		14 (70)
> 6 months		6 (30)

IFOVM: ifosfamide, etoposide, methylprednisolone; n. v.: normal value; IPI: international prognostic index; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; Mega-CHOP: high dose cyclophosphamide, vincristine, doxorubicin, prednisone; MACOP-B: methothrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin; DLBCL: diffuse large B-cell lymphoma; PTCL: peripheral T-cell lymphoma.

famide 30 minutes before its infusion, 60% during the infusion of ifosfamide and 20% during 12 hours after its completion) and methylprednisolone (60 mg/m^2 on days 1 to 5). Glycosylated granulocyte colony-stimulating factor (G-CSF) at a dose of 5 mg/kg daily was started on day 6. After full hematologic recovery, two cycles of the DHAP regimen[9] (dexamethasone 40 mg days 1-4, cytarabine 2 g/m^2 every 12 hours as a 2-hour infusion and cisplatin 50 mg/m^2 by continuous infusion on days 1 and 2) were given as consolidation chemotherapy. Harvesting of peripheral blood stem cells (PBSC) was planned after either IFOVM or DHAP primed with G-CSF at a dose of 5 µg/kg daily. Patients who achieved complete remission (CR) or partial remission (PR) were to receive APBSCT with the BEAM protocol.[10]

Table 2. Response to IFOVM / DHAP according to the disease status during progression.

	CR	*PR*	*Overall response*
All patients (n=20)	3	8	11 (55%)
Refractory (n=14)	1	4	5 (36%)*
Relapsed (n=6)	2	4	6 (100%)*

*IFOVM: ifosfamide, etoposide, methylprednisolone; DHAP: dexamethasone, cytarabine, cisplatin; CR: complete remission; PR: partial remission; *p=0.02 by Fisher's exact test.*

Patient characteristics at treatment are summarized in Table 1. The median age was 50 years (range 31-64) with 11 men and 9 women. All patients showed dramatic tumor regression following IFOVM. Treatment was well-tolerated. The main toxicity was myelosuppression with neutropenia (less than 0.5×10^9/L) lasting a median of 4 (range 2-8) days and thrombocytopenia (less than 20×10^9/L) a median of 4 (range 0-32) days. Ten patients developed neutropenic fever with 2 bacteremias and one urinary tract infection. Non-hematologic toxicity according to the WHO scale was modest: 2 patients developed grade 2 neurologic toxicity, 1 grade 3 pulmonary toxicity, and 1 grade 3 hepatic toxicity, with full recovery in all cases. All 20 patients proceeded to receive DHAP consolidation: 2 patients received only one cycle, 15 two cycles and 3 three cycles. Following IFOVM and DHAP three patients achieved CR (15%) and 8 PR (40%), for a total response rate of 55%. Tumor progression during DHAP was noted in 9 patients. The total response rate appeared to differ between patients with relapsed and refractory disease, 6/6 (100%) in the former group vs 5/14 (36%) in the latter (p=0.02 by Fisher's exact test) (Table 2).

In 4 patients no attempt was made to collect PBSC because of rapid tumor regrowth during DHAP. In the remaining 16 cases PBSC were collected from 4 patients after IFOVM and from 12 after DHAP. In the former group the median number of CD34$^+$ cells harvested was 11.6×10^6/kg (range 3-15) from a median of 1 apheresis (range 1-2), while in the DHAP group a median of 6×10^6/kg CD34$^+$ cells (range 2.7-25.7) were harvested from 1 to 3 aphereses (median 2).

To date ten patients have been autografted (3 in CR, 6 in PR and 1 with progressive disease) and two in stable PR are awaiting transplantation. With a median follow-up after transplant of 13 months, 5 patients have progressed, 2 have died in apparent CR and 3 are still in CR, 25, 23 and 7 months after APBSCT. The median overall survival of this series, calcu-

lated from the beginning of salvage therapy, is 5 months (range 3-32).

In conclusion, this salvage regimen with high-dose ifosfamide and etoposide appears promising in patients with relapsed progressive NHL, and patient accrual will continue in this disease category. Both IFOVM and DHAP plus G-CSF allow adequate PBSC mobilization for one or two APBSCT procedures. In patients with refractory aggressive NHL the regimen appears to have little activity, and such patients should receive alternative experimental therapies.

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References

1. Aisenberg AC. Coherent view of non-Hodgkin's lymphoma. J Clin Oncol 1995: 13:2656-75.
2. Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993: 328:1023-30.
3. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin´s lymphoma. N Engl J Med 1993; 328:1002-6.
4. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329:987-94.
5. Cabanillas F, Hagemeister FB, Bodey GP, Freireich EJ. IMPV-16: an effective regimen for patients with lymphoma who have relapsed after initial combination chemotherapy. Blood 1982; 60:693-7.
6. Tigaud JD, Demolombe S, Bastion Y, Bryon PA, Coiffier B. Ifosfamide continuous infusion plus etoposide in the treatment of elderly patients with aggressive lymphoma: a phase II study. Hematol Oncol 1991; 9:225-33.
7. Bosly A, Coiffier B, Grisselbrecht C, et al. Bone marrow transplantation prolongs survival after relapse in aggressive-lymphoma patients treated with the LNH-84 regimen. J Clin Oncol 1992; 10:1615-23.
8. Philip T, Guglielmi C, Haagenbeek 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; 333:1540-5.
9. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988; 71:117-22.
10. Gaspard MH, Maraninchi D, Stoppa AM, et al. Intensive chemotherapy with high doses of BCNU, etoposide, cytosine arabinoside, and melphalan (BEAM) followed by autologous bone marrow transplantation: toxicity and anti-tumor activity in 26 patients with poor-risk malignancies. Cancer Chemother Pharmacol 1988; 22:256-62.

Transfusion requirement can be abolished by epoietin-α and autologous platelet predeposit in patients receiving high dose chemotherapy with stem cell support

In patients undergoing high dose sequential chemotherapy (HDS) for breast cancer (BC),[1] allogeneic platelet transfusions can be avoided by using cryopreserved autologous platelets.[2] Nevertheless, half of these patients develop a mild anemia before myeloblation, requiring eventually blood transfusion. In this cohort of patients, we evaluated the efficacy of recombinant human erythropoietin (EPO)[3,4] in preventing the development of anemia, and therefore any allogeneic transfusion requirement.

Sir,

Ten consecutive high risk BC patients undergoing HDS with PBSC transplantation entered the study. Relevant parient characteristics at baseline are reported in Table 1. HDS included high dose cyclophosphamide (HDCY, 7 g/m^2) plus G-CSF and, as the final myeloablative regimen requiring PBSC support ($\geq 5\times10^6$ CD34$^+$ cells/kg bw), melphalan (160 mg/m^2) and thiotepa (600 mg/m^2). Platelet transfusions were given when the platelet count dropped below 20×10^9/L or in the presence of bleeding episodes while red blood cell (RBC) units were transfused for Hb level < 8 g/dL. Epoietin-α (EPO-α) was administered at a dose of 10,000 U sc three times weekly plus oral iron supplementation starting after PBSC collection until myeloablation.

Autologous PCs were collected by a single plateletpheresis at platelet rebound after HDCY, when circulating platelet count exceeded 250×10^9/L. PCs were processed, stored and reinfused as previously described.[2] All patients completed the HDS program.

Before HDCY the median serum EPO concentration was 19.8 mU/mL, and in 5/9 patients the O/P ratio was < 0.8, revealing an inappropriate serum EPO concentration for the degree of anemia.[5] EPO-α was administered for 7 to 9 weeks, without any adverse effect. Changes in Hb level during EPO-α treatment and transfusion requirement are reported in Table 2.

Table 1. Baseline iron status and hematologic parameters of our 10 patients. Data are reported as mean ± SD (range).

Age, yrs (median, range)	43 (34-54)
Hb, g/dL	12.3±1.4 (10.1-14.5)
Serum iron, µg/dL	81±40 (11-132)
Transferrin saturation %	29±19 (2-59)
Serum ferritin, mg/dL	130±187 (16-594)
Serum EPO, mU/mL	13±6 (3.4-19)
O/P log EPO ratio	0.8±0.2 (0.3-1.0)