II study. The regimen used had less severe toxicity compared to the regimen used by Lyss *et al.* [6] but response rates were also less when compared to their good marrow reserve group (26%) and were comparable to their poor marrow reserve group (14%). Microangiopathic side effects were not observed and the treatment was generally subjectively well tolerated. Because of the low toxicity observed in this study probably more intensive treatment could be used, but we doubt that substantial improvement in results in heavily pretreated breast cancer patients can be achieved.

Mitomycin plus vindesine in the dose and schedule applied has no place in the treatment of these patients.

1. Bonadonna G, Valagussa P. Chemotherapy of breast cancer: current views and results. *Int J Radiat Oncol Biol Phys* 1983, **9**, 279–297.
2. Petri E, Schmahl D. On the relevance of "second line" cytotoxic chemotherapy in patients with metastatic breast cancer resistant to standard chemotherapy. *Wien Klin Wochenschrift* 1986, **98**, 790–797.
3. Godfrey T. Mitomycin C: current status and new developments. In: Carter S, Crooke S, eds. New York, Academic Press, 1979, 91–99.
4. Currie V, Camacho F, Wittes R, *et al.* Phase II evaluation of vindesine in patients with advanced breast cancer. *Cancer Treat Rep* 1980, **64**, 693–695.
5. Garewal HS, Brooks RJ, Jones SE, *et al.* Treatment of advanced breast cancer with mitomycin-C combined with vinblastine or vindesine. *J Clin Oncol* 1983, **1**, 772–775.
6. Lyss A, Luedke S, Einhorn L, *et al.* Vindesine and mitomycin C in metastatic breast cancer. *Oncology* 1989, **46**, 357–359.

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Continuous Infusion of Interleukin-2 in Two Relapsed High Grade Non-Hodgkin Lymphoma Patients: Effectiveness and Tolerability

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THE ANTITUMOUR effect of interleukin 2 (IL-2) and lymphokine activated killer (LAK) cells has been extensively studied in experimental models and in clinical trials, including in patients with various types of solid tumours [1–3] and, more recently, in patients with haematological malignancies such as acute leukaemias [4–6] and lymphomas [7].

We report here on 2 high grade non-Hodgkin lymphoma (HG-NHL) patients, relapsed after several intensive chemotherapeutic programs, treated with IL-2 (Cetus Corporation, Emeryville, California), at a dose 3×10^6 Cetus Units/day by continuous infusion for 5 days, followed by 5 days off and by 5 further days of IL-2. This was repeated 3 times at 2 week intervals.

The first patient was a 28-year-old man with stage IIA bulky abdominal HG-NHL (centroblastic lymphoma according to the Kiel classification) [8] firstly treated with MACOP-B and, after relapse, with DHAP regimen. After 3 courses of this regimen, the therapy was stopped because of the haematological toxicity and of the poor clinical response. 4 months later IL-2 was started. During the first 5 days of therapy, the patient complained of profuse sweats, fatigue, fever, nausea, vomiting, diarrhoea, oliguria and mild renal dysfunction. There was a moderate weight gain and a transient increase of creatinine to a maximum of 3.5 mg/100 ml and bilirubin to 2.2 mg/100 ml. After the 5-day rest period, the patient started the second 5-day course of IL-2 therapy, but on the fourth day, the drug was stopped due to confusion, fever, sweats, hypotension and intense abdominal pain which worsened over 2 days. The patients underwent laparotomy and a right colonic necrosis/perforation, together with a diffuse involvement of the intestine by lymphoma, were observed. 2 days later the patient died. When the administration of IL-2 was stopped there had been a complete resolution of all superficial lymphadenopaties.

The second patient was a 30-year-old man with a diagnosis of a III stage B HG-NHL (large cell lymphoma Ki-1 positive according to the Kiel classification) [8] treated with MACOP-B regimen followed by abdominal radiotherapy (36 cGy). After 5 months, when the relapse occurred, the patient entered the IL-2 continuous infusion trial. During the therapy course, the patient had no significant complications except for moderate nausea and hypotension. Creatinine never increased, probably because of the prophylactic use of low dose dopamine by continuous infusion. At the completion of the second course, there was a 40% reduction in the previously measurable disease. Despite the acceptable toxicity and a measurable response, the patient refused to continue treatment with IL-2 or any other chemotherapy and died 3 months later.

In both patients haematològical and immunological effects were monitored before, during and after treatment with IL-2

Table 1. Lymphocyte subset analysis and functional studies assessed in the 2 patients before, during and after IL-2 treatment

	Pre IL-2		First course		First rest period		Second course		Second rest period	
Case	1	2	1	2	1	2	1	2	1	2
$\times 10^9/l$										
Ly	4731	725	538	504	1505	5024	661	950	/	2310
CD3	184	1017	319	282	511	2009	187	510	/	1085
CD4	85	276	70	100	165	401	108	236	/	438
CD8	61	776	204	156	240	1205	84	680	/	577
CD57	0	690	51	141	135	2411	80	668	/	1339
CD16	0	362	12	45	255	2160	201	735	/	993
CD25	0	34	0	15	30	200	72	102	/	115
% cytotoxicity (E:T = 50:1)										
NK	22	26	35	44	60	74	14	32	/	60
LAK	47	75	21	36	13	83	/	23	/	/

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and, as expected, there was an increase in the number of lymphocytes and an increase in the NK and LAK activity (Table 1). Although both patients stopped the treatment immediately after two courses, a reduction of the enlarged lymph nodes was observed confirming the effectiveness of this treatment in these diseases.

The introduction of IL-2 based therapy into clinical haematology has resulted in the attainment of reproducible responses in malignancies refractory to more conventional therapeutic approaches. Thus, these results suggest and confirm the potential role of IL-2 in the treatment of malignant lymphomas. For the future, it is more likely that new protocols should be considered in an attempt to prevent relapse and prolong remission in lymphoma patients by eliminating the minimal residual disease.

1. Rosenberg SA, Grimm EA, McGrogan M, *et al.* Biological activity of recombinant human interleukin-2 produced in *Escherichia coli*. *Science* 1984, **233**, 1412–1415.
2. Rosenberg SA, Lotze MT, Muul LM, *et al.* A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. *N Engl J Med* 1987, **316**, 889–897.
3. Paciucci PA, Holland JF, Glidewell O, *et al.* Recombinant interleukin-2 by continuous infusion and adoptive transfer of recombinant interleukin-2 activated cells in patients with advanced cancer. *J Clin Oncol* 1989, 7, 869–878.
4. Lotzova E, Savary CA, Herberman RB. Induction of NK cell activity against fresh human leukemia in culture with interleukin 2. *J Immunol* 1987, **138**, 2718–2727.
5. Fierro MT, Liao XS, Lusso P, *et al.* *In vitro* and *in vivo* susceptibility of human leukemic cells to lymphokine activated killer activity. *Leukemia* 1988, **2**, 50–54.
6. Foa R, Meloni G, Tosti ??, *et al.* Treatment of residual disease in acute leukemia patients with recombinant interleukin 2 (IL-2): clinical and biological findings. *Bone Marrow Transplant* 1990, **6** (Suppl. 1), 98–102.
7. Allison MA, Jones SE, McGuffey P. Phase II trial of outpatient interleukin-2 in malignant lymphoma, chronic lymphocytic leukemia and selected solid tumors. *J Clin Oncol* 1989, 7, 75–80.
8. Lennert K. Classification of non-Hodgkin's lymphomas. In: Lennert K, *et al.* eds. *Malignant Lymphomas Other than Hodgkin's Disease: Histology, Cytology, Ultrastructure, Immunology*. Berlin, Springer 1978, 111–469.

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Correction

Chemoresistance in rat ovarian tumours — In this article by W. J. Zeller and colleagues (Vol. 27, No. 1) p. 64, the legend to Fig. 4 was incorrect. It should have read "DNA interstrand cross-links (ISCL) after exposure to cisplatin. Hatched column (right) = 0.342/DDP and striped column (left) = 0-342".