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A Phase II Study with Mitomycin and Vindesine in Metastatic Pretreated Breast Cancer

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COMBINATION CHEMOTHERAPY as initial treatment has shown response rates in metastatic breast cancers of 50–60%, with a median survival for responding patients of approximately 24 months [1]. In case of progression during or after multiagent chemotherapy, the likelihood of a durable second remission diminishes. In a meta-analysis of 85 clinical studies concerning second line chemotherapy of metastatic breast cancer the median remission rate ranged between 0–10% complete response (CR) and 20–40% partial response (PR) for the most commonly used second line chemotherapy modalities. The mean duration of response was 6 months [2]. Mitomycin [3] and vindesine [4] have shown in single drug therapy to be active in previously treated breast cancer. Combination of the two drugs has been reported to give 40% response rates, provided the dose of mitomycin exceeds 10 mg/m^2 per course [5]. Based on these data the Comprehensive Cancer Study Group Limburg (IKL) initiated a phase II study of mitomycin and vindesine for refractory breast cancer patients.

Patients were eligible if they had histologically proven metastatic breast cancer. Patients were required to have had an anthracycline consisting multiagent chemotherapy regimen either as palliation or as adjuvant treatment; they should not have received mitomycin and/or a vinca alkaloid. Life expectancy should exceed 12 weeks and age should be below 71 years. Progressive and measurable or evaluable disease, adequate bone marrow reserve and adequate kidney and liver function were required.

Patients with central nervous system disease (cerebral or meningeal metastases), a performance status below 50% and uncontrolled cardiac disease were excluded. Mitomycin was administered at a dose of 10 mg/m^2 on days 1 and 28 and subsequently every 8 weeks. Vindesine was given on 3 consecutive days (day 1: 1.5 mg/m^2, day 2 and 3: 1.0 mg/m^2) every 4 weeks. Dose modification for mitomycin and vindesine were based on leucocyte and platelet nadirs. Toxicity was rated according WHO criteria. Response to treatment was defined as follows: CR, the complete disappearance of all measurable disease; PR, at least 50% reduction in the sum of the products of perpendicular diameters of measurable disease, without the appearance of new disease; progressive disease (PD), at least a 25% increase in tumour size or appearance of new disease. Response duration was measured from the time of documentation of response, survival was measured from the date of registration on study until death.

27 patients entered the study. Patients characteristics are shown in Table 1. The median number of cycles per patient were three (range 1–12), 4 patients recieved only 1 course because of PD during the first course, 7 patients received 2 courses. All these patients are included for response evaluation. Dose reduction was necessary in 3 patients; 2 patients received 20% less mitomycin because of myelosuppression; 1 patient got 50% less vindesine because of neurotoxicity.

Table 1. Patients' characteristics

No. of patients	27
Age	
Mean	52.5 y
Range	33–68 y
Sites of disease	
Bone	16
Liver	5
Lung/pleura	14
Lymphnode	8
Soft tissue (skin)	8
Previous chemotherapy	
Doxorubicin/epirubicin containing regimen	27
Only palliative	7
Adjuvant + palliative	7
Only adjuvant	8
Neo adjuvant	5

As shown in Table 2, granulocytopenia was the most important side-effect, and no septic periods were recorded. There was 1 CR, PR was achieved in 2 patients, stable disease (SD) in 6 patients and PD in 17 patients. 1 patient died after the first course of chemotherapy because of PD. The overall response rate was 11% (95% confidence limits 0–22%). The patient who attained a CR on vindesine plus mitomycin was previously treated in the adjuvant setting with doxorubicin containing multidrug regimen. The 2 patients with PR were previously treated for metastatic disease. The median duration of survival of the total group of patients was 5 months. 3 patients survived more than 1 year.

The expectation that a combination of two agents effective as single drug therapy in metastatic breast cancer would substantially improve the response rate did not come out in this phase

Table 2. Toxicity of mitomycin-vindesine regimen

	WHO 2 (%)	WHO 3 (%)	WHO 4 (%)
Leucocytes	30	7	0
Granulocytes	21	17	8
Haemoglobin	4	7	4
Nausea	0	9	0
Vomiting	17	4	0
Alopecia	0	27	13

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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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