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## **Fludarabine: risk factor for aggressive behaviour of squamous cell carcinoma of the skin?**

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and differentiate them from other conditions in order to institute the appropriate treatment, if this is possible.

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## Fludarabine: risk factor for aggressive behaviour of squamous cell carcinoma of the skin?

Fludarabine, a purine analogue, is effective in the therapy of low-grade non-Hodgkin's lymphomas. Side-effects include fever, peripheral neuropathy, pulmonary toxicity and significant depletion of T-lymphocyte populations. In addition, flare up and aggressive behaviour of squamous cell carcinoma (SCC) during fludarabine therapy has been observed [1].

We report on a 65-year-old patient with a lymphocytic B-cell lymphoma (stage IVA) diagnosed in 1997. Owing to an excess of blasts he was treated according to the German consensus protocol for aggressive non-Hodgkin's lymphoma. However, three cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) chemotherapy and two cycles of salvage therapy with holoxane, cytosar and vepeside did not produce a response, and led to complications such as *Candida* esophagitis and generalised herpes zoster infection. Owing to progressive lymphadenopathy and lymphocytosis, the patient was treated with four cycles of chlorambucil and prednisone, showing again minimal

response. In 2001, six cycles of fludarabine led to a near complete remission with reduction of all lymph node manifestations and normalisation of peripheral lymphocyte counts. Since the patient's disease progressed again, a combined immunochemotherapy with rituximab and fludarabine was initiated in autumn 2002. Again, a near complete clinical remission was achieved. However, within 2 weeks of the fourth therapy cycle, the patient developed a well-circumscribed nodule on the right cheek. The tumour impressed with a diameter of 1 cm and a centrally located horn plug.

Histology showed a well demarcated invasive proliferation of epithelial cells with squamous differentiation, extending into the dermis, a perineural invasion by tumour cells and lymphohistiocytic infiltration at the margins of the neoplasm. Immunohistochemistry revealed that the majority of the infiltrating lymphocytes were CD3+ CD4+ T-helper cells, whereas a few cells expressed CD8 antigen. Complete excision of the lesion was conducted and confirmed by micrographic work-up of the specimen. Two months later the patient presented with regrowth of the tumour. Again, total excision was performed resulting in two further recurrences within the following 3 months. Nine months after local consolidating radiotherapy (51 Gy) no further recurrence had occurred.

Although differential diagnosis of keratoacanthoma was considered initially, the histological features of perineural invasion and infiltrative tumour strands, as well as repeated tumour recurrence, strongly suggested the diagnosis of SCC [2, 3]. However, aggressive behaviour of the tumour led to the question of whether in this immunocompromised patient human papilloma viruses (HPV), especially HPV 5 and 8, might be involved in the development and unusual clinical course of skin cancer [4]. Accordingly, we performed a nested PCR, but did not detect the suspected HPV-specific sequences in the biopsy tissue. Non-Hodgkin's lymphomas on their own or fludarabine may be responsible for the increased incidence and aggressive behaviour of SCC in these patients [5]. Thus, we assume that the altered immune status in this patient was aggravated by concomitant fludarabine-induced T-lymphocyte depletion, which thereby facilitated the growth and aggressive behaviour of this secondary malignancy [6]. Careful examination of patients at risk will be warranted in order to detect secondary malignancies early and to treat them extensively.

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## Can HER2 overexpression predict response to pegylated liposomal doxorubicin in metastatic breast cancer patients?

We conducted a phase II clinical trial to determine the clinical efficacy and safety of pegylated liposomal doxorubicin in combination with gemcitabine as a first- or second-line treatment option in patients with metastatic breast cancer [1]. Based on a previous phase II study [2], the recommended dose was pegylated liposomal doxorubicin 25 mg/m<sup>2</sup> intravenously (i.v.) on day 1 and gemcitabine 800 mg/m<sup>2</sup> i.v. on days 1 and 8, every 21 days. A total of 41 patients were entered into the study between February 2003 and April 2004. The demographic and baseline clinical characteristics of all patients are listed in Table 1. Forty-one patients were assessable for response. The overall objective response rate (ORR) was 51% [95% confidence interval (CI) 35.9% to 66.5%], with one complete response (CR) (2.5%) and 20 partial responses (PRs) (48%). Eleven patients (27%) had evidence of stable disease (SD), and the remaining nine patients had disease progression (22%).

Nineteen women had HER2-overexpressing (2+/3+; Dako Herceptest) breast tumors, while in the other 19 patients breast cancer did not overexpress HER2 (0/1+). HER2 overexpression score 2+ showed amplification at the DNA level detected by fluorescence *in situ* hybridization. In three patients HER2 expression was not assessed. Concerning patients with HER2-positive tumors, 68% experienced a response (13 patients; one CR and 12 PRs), while 15.7% had evidence of SD (three patients) and 15.7% (three patients) had disease progression. Conversely, among women with HER2-negative tumors, the ORR was half that observed in HER2-positive cases (31.5%, all PRs), with a rate of SD and PD of 42% (eight patients) and 26% (five patients), respectively. Sixty-one per cent of patients with HER2-positive disease were endocrine responsive

**Table 1.** Characteristics of the patients

Characteristic	
Total patients	41
Median age, years (range)	55 (33–71)
Pre-/post-menopausal status	4/37
Hormonal receptor status	
ER+/PgR+	21
ER–/PgR–	16
ER+/PgR–	3
ER–/PgR+	1
Grading	
Grade 1	6
Grade 2	15
Grade 3	20
HER 2 (Dako Herceptest)	
0/1+	19 (14/5)
2+/3+	19 (9 <sup>a</sup> /10)
Unknown	3
Predominant metastatic sites	
Visceral	34
Bone/soft tissues	7
No. of metastatic site	
1	30
≥2	11
Previous anthracycline treatment	13
Adjuvant	9
Metastatic	4

<sup>a</sup>Amplification at DNA level detected by fluorescence *in situ* hybridization.

ER, estrogen receptor; PgR, progesterone receptor.

(estrogen receptor and/or progesterone receptor positive tumors). Among 13 women who achieved a response to pegylated liposomal doxorubicin plus gemcitabine combination, seven were chemotherapy naïve for metastatic disease, while six had previously received chemotherapy. Responses were also observed in six out of 13 patients with previous anthracycline exposure, with a PR rate of 46%.

No data on the predictive value of HER2 expression regarding response to gemcitabine in breast cancer are currently available. It has been reported that the gemcitabine–cisplatin interaction is more active than the etoposide–cisplatin interaction in lung cancer cells with high p185neu expression [3]. Elevated levels of HER2 extracellular domain adversely affect the efficacy of paclitaxel plus gemcitabine in advanced breast carcinoma [4].

Our findings seem to support, even considering the low number of patients recruited, a positive interaction between HER2 overexpression and sensitivity to pegylated liposomal doxorubicin, substantially confirming the sensitivity of