Anti-Cancer Drugs 1997, **8**, pp. 643–644

Letter to the editor

Weekly short infusions of gemcitabine are not associated with suppression of lymphatic activity in patients with solid tumors

Thomas Daikeler, Kathrin Maas, Jörg Thomas Hartmann, Lothar Kanz and Carsten Bokemeyer

Department of Internal Medicine II, Hematology/Oncology, University of Tübingen, Germany.
Tel: (+49) 7071 298-7121; Fax (+49) 7071 293-675.

Key words: CD4/CD8 ratio, Gemcitabine, infection, lymphocytes, solid tumors.

Gemcitabine is a novel pyrimidine antimetabolite with antineoplastic activity against a wide range of solid tumors including metastatic pancreatic carcinoma, non-small cell lung cancer (NSCLC), ovarian and breast cancer. Recently we reported activity in platinum-resistant germ cell cancer.[1] Common side effects of gemcitabine are nausea, vomiting, a flu-like syndrome with fever, rash, and leucocytopenia and thrombocytopenia. These side effects are rather mild and rarely exceed WHO grade II toxicity, except for myelosuppression. Severe infections (WHO grade III/IV) have been reported in less than 1% of the patients receiving gemcitabine.[2] In contrast, treatment with pyrimidine analogs like fludarabine or cladribine, which have demonstrated activity in low-grade lymphoma and chronic lymphatic leukemia,[3] is associated with a risk for severe infections due to suppression of the functional lymphatic tissue.[4] A suppression of the CD4/CD8 ratio has been observed already after two courses of fludarabine treatment.[5] It has not been previously demonstrated whether gemcitabine may cause similar alterations of lymphatic tissue. Therefore we investigated the effect of gemcitabine on different lymphocyte subsets during consecutive applications.

Sixteen patients with solid tumors (three NSCLC, three pancreas, three testicular, two breast, one ovarian germ cell, one ovarian, one small cell lung, one gastric cancer and one carcinoma of unknown primary), 15 of whom were previously treated, received at least three applications of gemcitabine (1000 mg/m^2 as a 30 min infusion, at days 1, 8, 15; q 4 weeks). Therapy was stopped in all patients when disease progression was documented by radiological, serological or clinical evidence, or in case of severe non-hematological organ toxicity (WHO grade III/IV). In case of hematological toxicity WHO grade III/IV, therapy was delayed until hematological values had recovered to normal ranges. Lymphocyte surface antigens were analyzed by standard technique flow cytometry prior to every infusion.

The median number of gemcitabine applications was 6 (range 3–13). The median number of leukocytes before therapy was 7823/μl, with lymphocytes 875/μl, including 68% T cells ($CD3^+$), 9% B cells ($CD19^+CD20^+$) and 15% NK cells ($CD56^+CD16^+CD3^-$), and the CD4/CD8 ratio was 1.7. Within 2–3 weeks after gemcitabine therapy the median number of leukocytes of all patients was 5136/μl, with lymphocytes 1012/μl, including 77% T cells, 8% B cells and 10% NK cells, and a CD4/CD8 ratio of 2.2 (Table 1). A decrease of the CD4/CD8 ratio during gemcitabine therapy was excluded on the 95% significance level. Side effects of gemcitabine therapy were generally mild, mostly nausea (four patients), thrombocytopenia grade II and IV (two patients), and leukocytopenia grade III (two patients). Severe infectious complications or opportunistic infections were not seen in these 16 patients.

In summary, gemcitabine did not reduce the CD4/CD8 ratio and NK cell number in our patients with solid tumors during weekly treatment, and in addition no severe infectious complications were observed. These data indicate that gemcitabine is a safe antineoplastic agent not associated with severe and long-lasting immunosuppression when used in a

Correspondence to C Bokemeyer

Table 1. Mean lymphocyte counts and analysis of the lymphocyte subpopulations in 16 patients before and after three or five applications of gemcitabine (95% confidence intervals in parentheses): no significant alteration occurred during or after gemcitabine application

	Gemcitabine applications		
	0	3	5
Patients	16	16	10
Lymphocytes (/μl)	875 (725–1250)	981 (701–1261)	938 (504–1372)
T cells (%)	68 (63–73)	74 (70–78)	75 (70–80)
CD4/CD8 ratio	1.7 (1.2–2.2)	2.1 (1.5–2.7)	2.5 (1.5–3.5)
B cells (%)	9 (5–13)	8 (5–11)	9 (5–13)
NK cells (%)	15 (11–19)	11 (9–13)	11 (8–14)

weekly short-infusional schedule. Thus standard antibiotic prophylaxis for gemcitabine-treated patients does not appear to be necessary.

References

1. Maas K, Daikeler T, Kanz L, Bokemeyer C. Activity of gemcitabine in platinum-resistant ovarian germ cell cancer. *Eur J Cancer* 1996; **32A**: 1437–8.
2. Green MR. Gemcitabine safety overview. *Semin Oncol* 1996; **23**: 32–5.
3. Pott-Hoeck C, Hiddeman W. Purine analogs in the treatment of low-grade lymphomas and chronic lymphocytic leukemias. *Ann Oncol* 1995; **6**: 421–33.
4. Boldt DH, von Hoff DD, Kuhn J, *et al.* Effects on human peripheral lymphocytes of *in vivo* administration of 9-β-D-arabinofuranosyl-2-fluoroadenine 5′-monophosphate (NSC 312887), a new purine antimetabolite. *Cancer Res* 1984; **44**: 4183–6.
5. Wijermans PW, Gerrits WBJ, Haak HL. Severe immunodeficiency in patients treated with fludarabine monophosphate. *Eur J Haematol* 1993; **50**: 292–6.

(Received 13 May 1997; accepted 21 May 1997)