Thrombocytosis in patients with pancreatic cancer treated with gemcitabine – does it have clinical significance? Description of 6 cases

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Gemcitabine is a cytostatic drug from the pyrimidine antimetabolite group. It is used in treatment of some neoplasms, among them inoperable pancreatic cancer. The most common undesirable effects of gemcitabine include pancytopenia, with thrombocytopenia associated with gemcitabine's myelosuppressive activity. This study contains a description of six cases of patients with pancreatic cancer treated with gemcitabine, who – contrary to expectations – showed increased levels of thrombocytes. The number of thrombocytes ranged from 424 to 1059×10^9 (mean 470×10^9). It was highest during the 2nd and 3rd chemotherapy cycles and it normalized after completion of treatment. One patient suffered from a cardiac infarction on the 15th day of the 3rd cycle of treatment, despite a normal level of thrombocytes on the day; however, the patient indicated thrombocytosis on the 1st day of the cycle. No thromboembolic complications were observed in the remaining patients. These patients were not subjected to any antithrombotic prophylaxis. The mechanism by which thrombocytosis occurs after administration of gemcitabine and the clinical significance of this fact remain unknown.

Key words: pancreatic cancer, thrombocytosis, gemcitabine, thrombosis.

Gemcitabine is a cytostatic drug from the pyrimidine antimetabolite group. It is a 2' deoxycytidine analogue, in which hydrogen atoms on the C2' carbon of deoxycytidine are replaced by fluorine atoms. Consequently, gemcitabine is built into the double helix of DNA instead of 2' deoxycytidine, which results in DNA synthesis disorders and finally in cell death. It is a phase-specific drug, acting during the S phase of the cell cycle. Registered indications for administration of gemcitabine are numerous and include treatment of the following neoplasms: non-small cell lung cancer, ovarian carcinoma, breast cancer, urinary bladder cancer and inoperable pancreatic cancer [1, 2]. Gemcitabine is administered by 30-minute intravenous infusion in monotherapy or combined with other drugs, most frequently cisplatin. The main undesirable effects of gemcitabine application include damage of bone marrow which is manifested by neutropenia and thrombocytopenia. Less common complications include fever, balding, nausea, vomiting, skin rash, shank oedema, dyspnoea and drowsiness. A very rare undesirable effect, occurring less than once in 10 000 cases, is thrombocytosis [1, 2]. We noted that the frequency of its occurrence may be underestimated, because out of 60 patients with pancreatic cancer treated with gemcitabine in our clinic, in the last two years we observed thrombocytosis in about a dozen of them. Below we present a description of the six most representative cases.

Case description

The description refers to six patients receiving gemcitabine (Gemzar, Eli Lilly) in a standard dose of 1000 mg/m^2 on the 1st, 8th and 15th day of a 28-day cycle (one patient was subjected to combined treatment with erlotinib 100 mg/d) for pancreatic cancer, treated in the Department of Haematology and Oncology, Medical University of Warsaw in 2010, who demonstrated thrombocytosis after administration of Gemzar. The group consisted of 2 men and 4 women aged 60–78 (mean age 67.1 years). For all patients this was first-line treatment. Before treatment the number or thrombocytes in all patients was normal. After administration of gemcitabine, the number of thrombocytes increased above the norm assumed at the local laboratory at 400×10^9/l, reaching the highest values in the range from 424 to 1059×10^9/l (mean 470×10^9). The highest increase in the number of thrombocytes was observed on the 1st and 8th days of the second and third cycle of chemotherapy. The mean number of thrombocytes on the 1st day of the second cycle of chemotherapy was 535×10^9/l (range $319–1013 \times 10^9$/l), and on the 8th day of the cycle it was $490 \times \times 10^9$/l (range $342–608 \times 10^9$/l). Analogically, the values for the third cycle were 546×10^9/l (range $247–829 \times 10^9$/l) on the 1st day and 547×10^9/l (range $223–1059 \times 10^9$/l) on the 8th day. On the 15th day of each cycle the num-
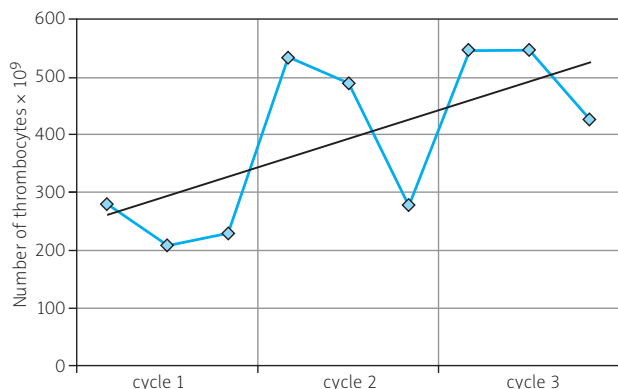
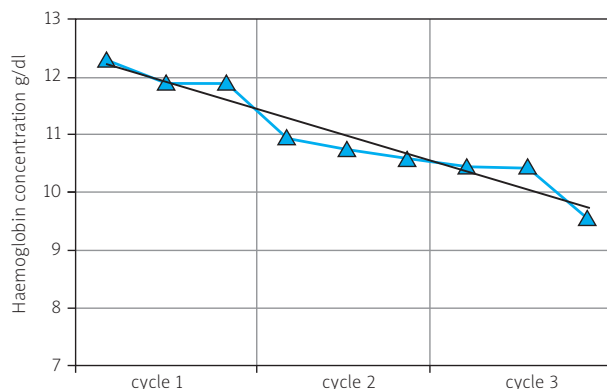**Fig. 1.** Number of thrombocytes during 3 cycles of Gemzar chemotherapy

Fig. 2. Hemoglobin concentration during 3 cycles of Gemzar chemotherapy

ber of thrombocytes decreased and reached mean values of 229 in the first cycle, 278 in the second cycle and 426×10^9/l in the third cycle. The data are shown in Fig. 1. For comparison, Fig. 2 shows haemoglobin behaviour in those patients on the same days. As expected, haemoglobin concentrations indicated a falling tendency in subsequent courses. The patients were administered from 4 to 6 chemotherapy courses. After termination of treatment with gemcitabine, the number of thrombocytes fully normalized and did not increase in further observation. Some patients were not subjected to further cytostatic treatment, but two patients underwent second-line treatment with the FOLFOX4 scheme (5-FU, oxaliplatin, leucovorin) during which thrombocytosis was not observed. One of the six studied patients indicated thromboembolic complications in the form of cardiac infarction which occurred on the 15th day of the third cycle of Gemzar. On this day the number of thrombocytes in this patient was normal at 151×10^9/l, but on the 1st day of the cycle it was above the norm at 454×10^9/l, and the highest number was observed on the 1st day of the second cycle – 478×10^9/l. History data taken earlier indicated no coronary heart disease. The other patients indicated neither thromboembolic complications nor acute coronary episodes. None of the six patients was subjected to antithromboembolic prophylaxis.

Discussion

Thrombocytosis often accompanies neoplastic diseases, especially lung and pancreatic cancer, and is connected with the tumour's production of cytokines stimulating megakaryopoiesis. However, typically in patients actively treated with chemotherapy, the number of thrombocytes decreases as a result of myelosuppressive activity of commonly applied cytostatic drugs. A considerable percentage of patients have a problem with thrombocytopenia at a certain stage of treatment, which delays administration of chemotherapy or even forces abandonment of further treatment. This is a common occurrence in patients with pancreatic cancer treated with gemcitabine, who often have to discontinue treatment because of haematological toxicity and a decrease in the number of thrombocytes below 100×10^9/l.

However, we observed that some patients actively treated with gemcitabine indicate – contrary to expectations – various degrees of thrombocytosis, defined as an increase

in the number of thrombocytes above 400×10^9/l. This occurrence is not common, but it is reported in the literature [3]. Some of such reports were presented at the ASCO Conference in 1998 and 2006 [4]. The reason for such a seemingly paradoxical reaction of increased numbers of thrombocytes after administration of gemcitabine is not known. As one possible explanation, other authors mention the phenomenon of production rebound after the period of thrombocyte nadir, because occurrence of thrombocytosis in improving patients with thrombocytopenia is common. Our observations indicate that patients treated with gemcitabine had the lowest number of thrombocytes on the 15th day of the first chemotherapy cycle (range 94-313 $\times 10^9$/l; mean 229 $\times 10^9$/l), and the increase began on the 1st day of the second cycle, which indeed may be associated with the rebound mechanism. The highest values of thrombocytes were observed during the second and third cycles of Gemzar, and in two patients the values exceeded 1000×10^9/l. A similar occurrence was observed in patients with lung cancer treated with the gemcitabine-vincristine scheme [5]. The question about clinical validity of this fact still remains unanswered. Contrary to the almost threefold higher risk of venous thrombosis in patients with thrombocytosis diagnosed before commencement of treatment, confirmed in a few studies [7, 8], in most reports – though they are not numerous – thrombocytosis after administration of gemcitabine was temporary and passed without complications. An exception to this rule is a study by Zecchina *et al.*, who assessed thromboembolic risk in patients with lung cancer treated with various chemotherapy schemes, where thrombocytosis was observed only in those after administration of gemcitabine, and thromboembolic complications occurred in four of them [6]. One of the six described patients suffered from a cardiac infarction, with the number of thrombocytes on that day at a normal level, even at the lower limit of the norm, whereas during the earlier period it was slightly over the norm ($< 500 \times 10^9$/l). Earlier the patient had not been diagnosed with heart disease. The other patients, often with significant thrombocytosis (maximum 1059×10^9/l), did not reveal any complications. This would suggest a lack of direct correlation between the degree of thrombocytosis and the presence of complications, or alternatively an impact of other factors on vascular complications. In the mentioned study by

Zecchina *et al.* no aberrations were observed in the coagulation system in patients with thrombocytosis after gemcitabine who developed thrombosis. However, the study did not assess the part played by functional disorders of thrombocytes, which are common in the course of neoplasms and can intensify under the influence of cytostatic drugs [6]. No literature has been found to assess the impact of gemcitabine on the function of thrombocytes. The value of undertaking such studies is not clear, but they might help in realistic assessment of thrombocytosis after administration of gemcitabine and in distinguishing a patient group requiring anti-aggregate treatment. It should also be mentioned that all cases of thrombocytosis after gemcitabine which we found in the literature relate to lung cancer, but one cannot rule out that in patients with pancreatic cancer or another neoplasm, the type of haemostatic disorders and the impact of treatment on cooperation of haemostasis components is completely different.

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