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The Absence of Influence of Acetylsalicylic Acid (ASA) on the Transient Decrease in Platelet Counts Observed after Infusion of Bleomycin and Vinblastine

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Abstract—*Retrospectively we observed an early-onset transient decrease in platelet counts in a group of patients treated with cisplatin, vinblastine and bleomycin. Though less pronounced, the decrease was also found in a prospectively studied group of patients treated with bleomycin, etoposide and cisplatin, but was absent after treatment with etoposide ad cisplatin. In a randomized cross-over study acetylsalicylic acid (ASA) appeared not to prevent the drop in platelet counts. Bleomycin appears to induce an early-onset transient decrease in platelet numbers, possibly by direct or indirect platelet lysis. Vinblastine may have a synergistic effect to this phenomenon.*

INTRODUCTION

A RAPID decrease in platelet counts has been reported following single agent bleomycin treatment [1], as well as following several bleomycin-including combinations of chemotherapy [2–11]. Though myelotoxicity and disseminated intravascular coagulation could be excluded [7], the cause of the rapid decrease remains obscure. It is postulated that vascular endothelial injury and activated platelet aggregation, resulting in reduced platelet survival [5], are involved in the observed decrease [7]. The present report includes additional data on the role of bleomycin in the observed early-onset transient decrease in platelet counts, as well as the results from a study on the influence of platelet-aggregation inhibition by acetylsalicylic acid (ASA) on the decrease.

MATERIALS AND METHODS

The first part of the study included a retrospective analysis in 17 male patients, aged 23–62 yr (median, 34 yr), on daily platelet counts until 4 days after bleomycin administration. Data were available for a total of 60 courses of treatment. These patients (group I) had been treated with vinblastine 0.15 mg/kg i.v. on days 1 and 2, bleomycin 30 mg i.v. on day 2 and cisplatin 20 mg/m^2/day i.v. on days 1–5 (PVB).

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For groups II and III platelet counts were studied prospectively.

Group II consisted of six male patients, aged 20–53 yr (median, 31.5 yr), treated with VP–16 (Etoposide) 120 mg/m^2 i.v. on days 1, 3 and 5, bleomycin 30 mg i.v. on day 2 and cisplatin 20 mg/m^2/day i.v. on days 1–5 (BEP).

In a total of 20 courses, daily platelet counts were taken similar to group I. For the sake of uniformity the day of bleomycin administration in groups I and II was stated as day 0.

Group III consisted of six male patients, aged 22–46 yr (median, 29.5 yr), studied for a total of 16 courses. They were treated with VP–16 120 mg/m^2 i.v. on days 1, 3 and 5 and cisplatin 20 mg/m^2/day i.v. on days 1–5 (EP). Platelet counts were taken daily. For optimal comparison the second day of treatment was stated as day 0.

The decision to treat patients with BEP or EP depended on randomization on entering an EORTC trial comparing both treatment arms.

The second part of the study consisted of a randomized cross-over study in 12 patients (group IV), 11 males and one female, aged 14–56 yr (median, 26 yr), treated with PVB similar to group I. They were randomized to receive 500 mg of acetylsalicylic acid (ASA) orally 2 hr prior to bleomycin administration, either during the first and second course (group IV A) or during the third and fourth cycle of chemotherapy (group IV B). Platelet counts were taken daily. Again the day of bleomycin administration was stated as day 0. All patients were treated for germ cell tumors.

Platelet counts on day 0 were taken prior to bleomycin administration in groups I, II and IV and were always similar to the counts on the preceding day in all groups.

Bleomycin was always given as a 30-min i.v. infusion. The cumulative dose never exceeded 390 mg. Platelet counts were performed on a Coulter counter.

Statistical analysis was based on the mean platelet numbers on days 1–4, expressed as the percentage of the number on day 0. Two-sided *t*-tests were used in the analysis, taking 5% as the significance bound.

RESULTS

We found a rapid fall in platelet counts in group I, with a nadir on days 2–3 (Table 1, Fig. 1). In Table 1 the mean per patient indicates the mean relative platelet count per patient, calculated over 1–5 courses. Only three out of 17 patients had a lower mean platelet count on day 4 as compared to day 3. This indicates recovery ($P = 0.013$) after the rapid decrease. In group II, where vinblastine had been replaced by VP–16, we obtained a similar decrease in platelet numbers, though less pronounced (Table 2, Fig. 1). Additionally, in group III, leaving out the bleomycin, no change in platelet counts could be noted during the initial 4 days after treatment (Table 2, Fig. 1). The difference on the mean platelet counts between groups II and III was significant ($P = 0.002$), with a 95% confidence interval for the mean platelet level after BEP of 79–97% (Table 2).

In the randomized cross-over study (group IV) we observed a similar decrease in platelet counts to that found in the retrospectively studied group I (Fig. 2). In group IV one patient was not evaluable because of a change in treatment after two cycles. In the remaining patients a significant effect of ASA was not observed (Table 3). Though the main difference appeared between treatment cycles 1 + 2 and 3 + 4, this was also non-significant.

DISCUSSION

Bleomycin is known not to be myelosuppressive [12–15], but the drug may cause an early-onset transient decrease in platelet counts [1–8]. Our observations in patients treated with PVB (groups I and IV) confirm previously reported similar studies [3–5]. However, the absence of a control group does not permit us to conclude from this part of the study that bleomycin is the sole inducing agent. Especially vinblastine has been suggested to be synergistic [6]. Therefore we also studied a similar group of patients, treated with BEP (group II), exchanging the vinblastine of PVB, for VP–16. Although the rapid decrease in platelet counts was also seen in these patients, it was less pronounced (Fig. 1), again suggesting synergism between vinblastine and bleomycin. Synergism between cisplatin and bleomycin has been excluded in a previous study [7]. Additionally, in the group of patients treated with EP (group III), leaving out bleomycin, the early-onset decrease in platelet counts completely disappeared. In our opinion these results indicate that the phenomenon can be attributed to bleomycin, confirming previous studies

Table 1. Mean (± S.D.) of relative platelet numbers in patients treated with PVB (group I)

	Treatment cycle				
	1	2	3	4	Mean per patient*
No. of patients	17	16	15	11	17
Day					
0	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)
1	65 (24)	61 (20)	67 (23)	63 (13)	64 (14)
2	57 (27)	47 (14)	54 (20)	52 (18)	52 (16)
3	54 (16)	48 (13)	57 (19)	51 (14)	52 (9)
4	65 (24)	54 (15)	65 (26)	55 (16)	60 (13)
Nadir	49 (14)	43 (12)	50 (20)	48 (14)	48 (11)
Day of nadir (No. of patients)					
0	—	—	—	—	
1	2	1	1	—	
2	9	8	10	5	
3	5	4	2	4	
4	1	3	2	2	

*The mean per patient indicates the mean relative platelet count per patient, calculated over 1–5 courses.

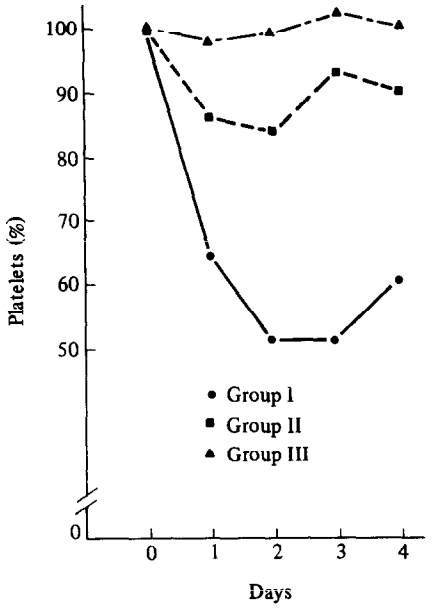

Fig. 1. Platelet counts, expressed as percentage of the number of platelets on day 0, in the study groups I III.

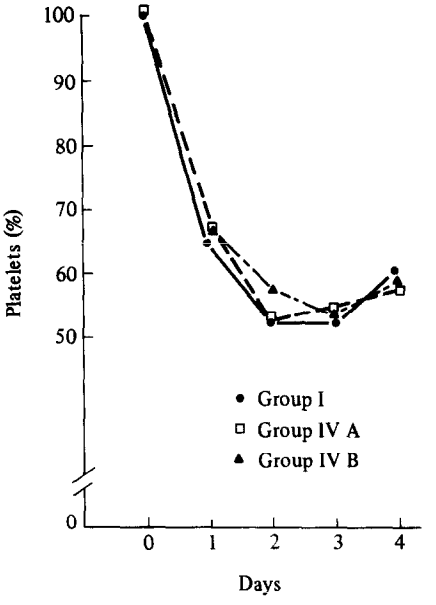

Fig. 2. Platelet counts, expressed as percentage of the number of platelets on day 0. Group I: without ASA; group IV A: first two cycles with ASA; group IV B: first two cycles without ASA.

Table 2. Nadir, day of nadir and mean (± S.D.) of the mean percentage of platelets on days 1–4, in patients treated with BEP or EP (groups II and III)

Treatment	Group II	Group III
No. of patients	6	6
Mean of days 1–4	88 (9)	98 (8)
Nadir	80 (6)	89 (11)
Day of nadir (No. of patients)		
0	0	1
1	1	2
2	3	0
3	2	1
4	0	2

Table 3. The effect of acetylsalicylic acid on the mean (± S.D.) percentage of platelets on days 1–4, in patients treated with PVB

	Group IV A	Group IV B
No. of patients	5	6
1st period	69 (9)	61 (9)
2nd period	54 (19)	56 (19)
Difference ASA vs control	15 (27)	−4 (26)

with single-agent bleomycin treatment [1]. The possibility of a similar effect of vinblastine alone cannot be excluded completely.

In the present study all patients received bleomycin intravenously, while in our previous study [7] it was administered intramuscularly. As the results are the same, the decrease in platelet counts is probably not dependent on the route of bleomycin administration.

Myelosuppression and disseminated intravascular coagulation have recently been excluded as the cause of the decrease in platelet counts [7]. However, reduced platelet survival time [5] and aggregation studies [7] suggest possible local platelet aggregation. For this reason we added 500 mg of ASA 2 hr prior to bleomycin administration. This dose of ASA has been shown to inhibit aggregation of platelets almost completely and immediately, lasting 24–48 hr [16]. The ASA was administered after randomization, the patients being their own control. In this group of patients (group IV) treated with PVB we observed a fall in platelet counts equal to group I. Addition of ASA appeared not to prevent the rapid decrease. Although this casts doubt on local aggregation as a cause of the early-onset decrease in platelet counts, it cannot be completely excluded that the decrease is caused by some local platelet aggregation that cannot be influenced by ASA. A possible explanation may be directly or indirectly induced platelet lysis. The latter may be triggered by known bleomycin-induced endothelial damage in pulmonary capillaries [9]. The recent postulation of Martin *et al.* [17] that platelets are produced by physical fragmentation of circulating megakaryocytes within the pulmonary circulation, is interesting within this context.

In conclusion, the present study confirmed the existence of a bleomycin-induced early onset transient decrease in platelet counts. The addition of ASA appears not to inhibit the occurrence of this decrease.

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