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Reduced Platelet Survival Following Chemotherapy with Vinblastine, Bleomycin and *cis*-Platinum for Testicular Teratoma*

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Abstract—*Patients receiving combination chemotherapy with vinblastine, bleomycin and cis-platinum for testicular teratoma frequently demonstrated early-onset transient thrombocytopenia. We have shown that this effect is due to reduced platelet survival. The relevant literature is reviewed and it is concluded that this phenomenon may be attributable to drug synergism.*

INTRODUCTION

COMBINATION chemotherapy with vinblastine, bleomycin and *cis*-platinum has greatly improved the results from treatment of metastatic testicular teratoma [1]. Toxicity from regimes comprising this combination is well-recognized, particularly nausea and vomiting, alopecia, fever, myelosuppression and neurotoxicity. Acute renal damage from *cis*-platinum can be avoided by pre-hydration and the induction of diuresis.

We observed frequent early-onset transient thrombocytopenia in patients treated with this drug combination, which sometimes interfered with adherence to the treatment protocol. This communication describes the phenomenon and investigations performed to elucidate the pathogenesis. The relevant literature is reviewed and possible mechanisms discussed.

MATERIALS AND METHODS

Patients

Twelve patients were studied (age range 21–39 yr). All had metastatic testicular teratoma.

Treatment

Treatment courses were given at 3 to 5-week intervals, usually every 4 weeks. Each course incorporated vinblastine on days 1 and 2 (total dose 12–28 mg, usually 20 mg); bleomycin on day 1 or divided between days 2–4 (total dose 30–90 mg, usually 90 mg); and *cis*-platinum on day 1 or divided between days 1–5 (total dose 125–175 mg).

Laboratory tests

Daily full blood counts were performed on all patients throughout each course.

Platelet survival studies were performed on four patients using the isotope ^{111}Indium ([^{111}In]), as indium oxime. The method of Scheffel *et al.* [2] was used. A normal range had previously been established with this method in our laboratory.

Platelets were labelled and injected immediately prior to chemotherapy on day 1. Samples were then collected daily for five days and counted together on the fifth day. Results were plotted on standard graph paper to determine the $t_{\frac{1}{2}}$ of indium-labelled platelets. Two patients had repeat survival studies performed two weeks later, between courses of chemotherapy. In one patient a gamma camera lung scan was performed one day after the injection of indium-labelled platelets.

Routine platelet adhesion and aggregation studies were carried out on the same four patients before and during chemotherapy. Adhesion was measured using the commercial 'Adeplat' kits. Aggregation was tested with Stago Collagen, ADP 1 and 10 μm, Ristocetin, Diamed Collagen and Hormo-Chemie Collagen in duplicate with normal controls.

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In vitro *studies*

Fresh platelets from normal donors were incubated with the combinations of vinblastine + bleomycin and vinblastine + *cis*-platinum, as well as with each of the three drugs as single agents, all in therapeutic serum concentrations. Each set of incubated platelets was then subjected to adhesion and aggregation studies, as above.

RESULTS

Eleven of the twelve patients demonstrated on at least one occasion a decrease in the peripheral blood platelet count of 50% or more by day 4, i.e. three days after the initiation of the course. The twelfth patient demonstrated a decrease of 50% by day 5. In a total of 30 studied courses received by the 12 patients, there was a decrease in the platelet count of $> 50\%$ by day 4 in 24 courses and by day 3 in 17 courses. In 12 courses there was a fall in the platelet count to 50×10^9/l or less. No haemorrhagic manifestations were seen. The mean daily platelet counts for all 30 courses are shown in Fig. 1.

Rapid recovery followed cessation of each course of chemotherapy, pre-treatment levels usually being attained within seven days. Leucocyte counts were also depressed, but more slowly.

This transient early-onset thrombocytopenia appeared to be uninfluenced by variations in the dosage and timing of the regime, and by whether or not patients had received prior radiotherapy. It was often observed on the first course of treatment.

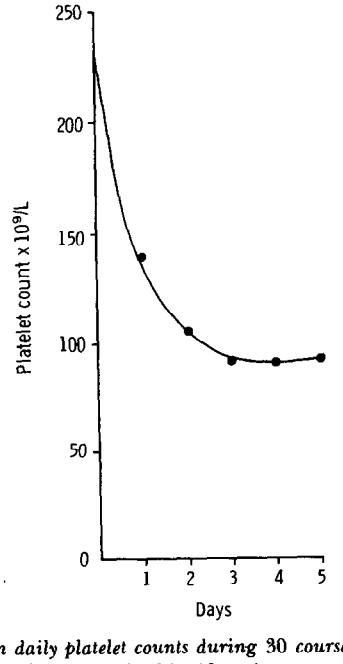

Fig. 1. Mean daily platelet counts during 30 courses of chemotherapy received by 12 patients.

Platelet survival studies

All four patients showed reduced platelet survival during chemotherapy, with values for $t_{\frac{1}{2}}$ [^{111}In] of 30, 38, 45 and 48 hr (normal value in this laboratory is 96–110 hr) (Fig. 2). In Fig. 3 we have plotted for one patient the platelet counts and survival curve together. Repeat platelet survival studies performed in two patients in between courses of chemotherapy yielded results for $t_{\frac{1}{2}}$ [^{111}In] of 92 and 98 hr.

Platelet adhesion and aggregation studies

No abnormality in adhesion was detected, either in samples from patients or in the *in vitro* studies. Two of the patients showed failure to aggregate with Stago Collagen during chemotherapy, but aggregation was normal with other commercial collagen preparations. All other aggregation was normal. We could demonstrate no abnormality of aggregation of platelets from normal donors following incubation *in vitro* with any of the single drugs or combinations.

Lung scan

No isotopic uptake in the lungs was demonstrated in the one patient scanned.

DISCUSSION

Early-onset transient thrombocytopenia appears to be extremely common in patients receiving combination chemotherapy with vinblastine, bleomycin and *cis*-platinum. Because of rapid recovery, this effect may not be detected if blood counts are only performed weekly, as is probably often the case [3]. This phenomenon has previously been documented [4, 5], but this article describes the first clear demonstration that it is consequent on decreased platelet survival. This is important, because several of our earlier patients had chemotherapy courses terminated prematurely as a result of thrombocytopenia. However, as it became clear that this effect was transient, did not result in extremely low platelet counts or haemorrhagic sequelae and was not attributable to marrow failure, subsequent courses could usually be completed.

Wilkinson *et al.* attributed this effect to vinblastine [4], but reduced platelet survival does not appear to be a recognised feature of therapy with vinblastine, bleomycin or *cis*-

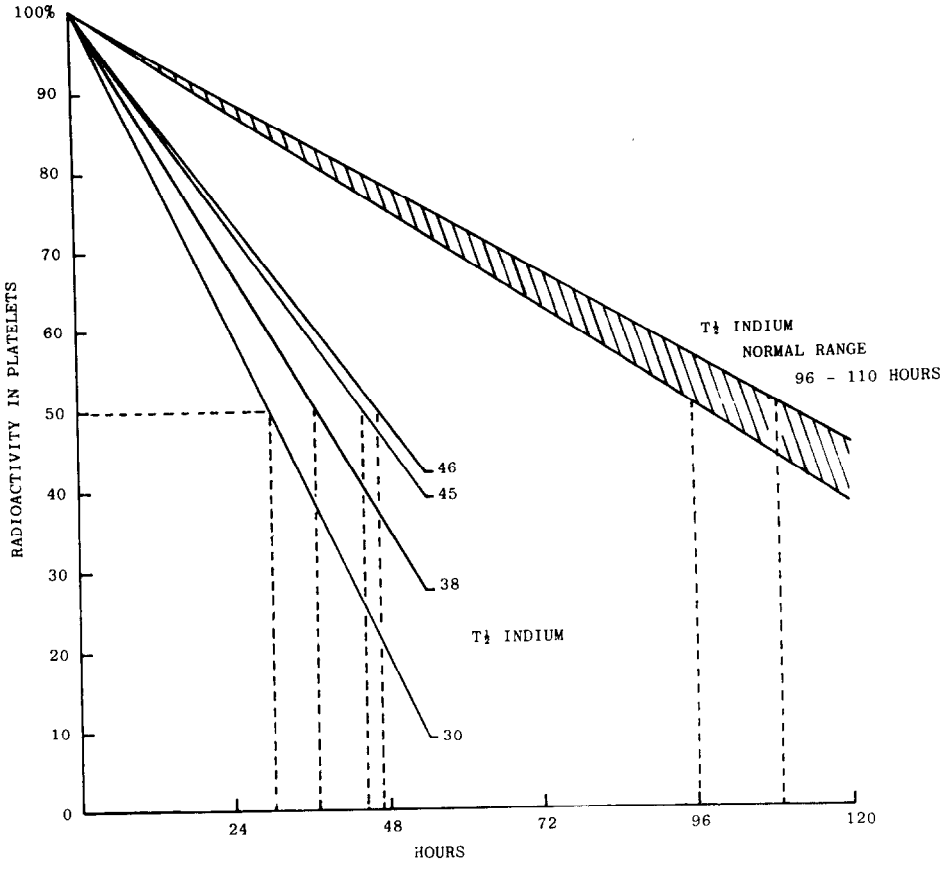

Fig. 2. Platelet survival in 4 patients during chemotherapy.

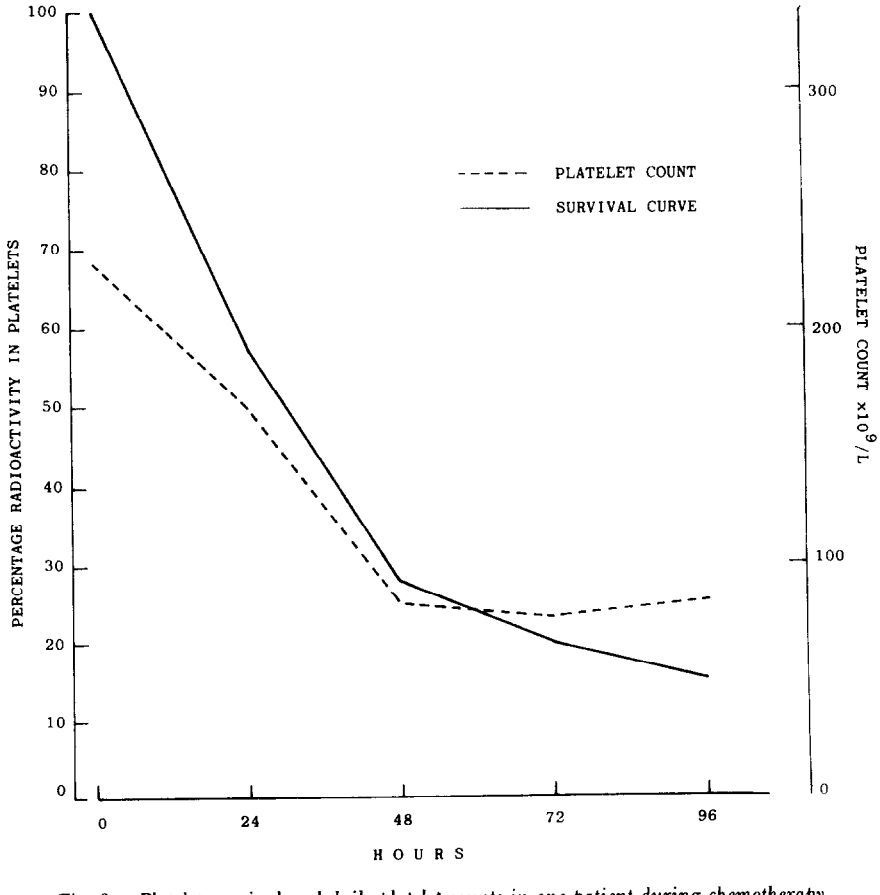

Fig. 3. Platelet survival and daily platelet counts in one patient during chemotherapy.

platinum as single agents, although it is, of course, recognised that all three drugs are capable of causing thrombocytopenia through myelosuppression.

In 21 of 22 patients given vinblastine as a single agent in doses of 0.15 mg/kg/day for three to four consecutive days, there was little or no depression of platelet counts [6]. Of 175 patients treated with bleomycin, 39% had some degree of thrombocytopenia, but the mean maximum depression of platelet counts occurred at day 11 [7]. The incidence of thrombocytopenia in 298 patients given *cis*-platinum as a single agent was 16%, nadirs being seen after 18–23 days [8].

We can find only one report of repeated early-onset thrombocytopenia with any of these drugs as single agents. Robert *et al.* described eight patients who demonstrated this phenomenon on treatment with bleomycin [9]. All had received intensive prior drug treatment, and in all but one instance, prior radiotherapy. They did not have a denominator for their eight cases, but in their original trial of bleomycin they found only a 20% incidence of haematological toxicity. It appears that their observation of thrombocytopenia was far less frequent than its occurrence amongst our patients.

There is therefore indirect evidence that this effect on circulating platelets is mediated through drug synergism. Early-onset thrombocytopenia has been previously described in patients given only vinblastine and bleomycin [10, 11], although Hilgard and Hossfeld ascribed it to bleomycin alone, invoking platelet sequestration in the lungs, consequent on early capillary endothelial damage. There was no direct evidence for this theory, or for increased platelet consumption, but they did satisfactorily demonstrate the absence of evidence for intravascular coagulation. We could demonstrate no uptake in the lungs of the single patient of ours on whom a scan was performed following injection of [^{111}In]-labelled platelets.

Early-onset thrombocytopenia does not appear to be a feature of combined *cis*-platinum and bleomycin therapy [12; Wolf, personal communication]. However, some of our patients demonstrated an appreciable fall in the platelet count by day 2 having received vinblastine and *cis*-platinum but no bleomycin. Thus if this effect on circulating platelets is mediated through synergism, then it may not necessarily be confined to a single combination of drugs, although vinblastine would appear to be a common factor. Unfortunately we were unable to demonstrate evidence for this hypothesis in *in vitro* studies, but a synergistic mechanism might be dependent on the known affinity of vinblastine for platelets, and its ability to damage and remove platelet microtubules [13].

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