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# Augmentation of Vincristine-induced Thrombocytosis by Norethisterone

BRIAN M. J. CANTWELL, RICHARD H. J. BEGENT* and ROBERT D. RUBENS†

*Imperial Cancer Research Fund Breast Cancer Unit, Guy's Hospital, London SE1 9RT, United Kingdom*

**Abstract**—*Seventy-five patients with advanced breast cancer were treated with adriamycin and vincristine in combination. An overall incidence of thrombocytosis (platelet count* ≧ *400,000) was observed in* 36 *patients* (48%). *This phenomenon was significantly more common in patients who were receiving a progestogen (norethisterone acetate) concomitantly* (71.4%) *compared with those not so treated* (27.5%).

## INTRODUCTION

VINCRISTINE, unlike most cytotoxic drugs, is not normally myelosuppressive and can cause an increase in the number of circulating platelets [1, 2]. This phenomenon has been exploited by using vincristine to treat thrombocytopenia [3]. In this paper we describe the occurrence of thrombocytosis in patients with advanced breast cancer receiving vincristine in combination with adriamycin, and how this phenomenon was augmented by concomitant progestogen treatment.

## MATERIALS AND METHODS

*Patients*

Seventy-five patients with advanced breast cancer were treated with combination chemotherapy in three-weekly cycles as follows: adriamycin 70 mg/m$^2$ (60 mg/m$^2$ in patients older than 60 yr, maximum dose 120 mg) on day 1 and vincristine 1.4mg/m$^2$ i.v. (maximum dose 2 mg) on days 1 and 8. After the maximum cumulative dose of adriamycin had been given (usually after 8 cycles) or, if progression of disease has occurred before then, treatment was changed to a combination of cyclophosphamide, methotrexate and 5-fluorouracil. Dose reductions were made if there was bone marrow suppression. In addition some patients were given norethisterone acetate 20 mg three times daily concomitantly with chemotherapy in a randomised trial to assess the contribution of this progestogen to chemotherapy [4]. Blood counts were done on days 1 and 8 of each cycle of chemotherapy and platelet counts were determined by either the method described by Eastham [5] or the Technicon method. Thrombocytosis is defined as a platelet count of ≧ 400,000/μl.

## RESULTS

Thrombocytosis was observed during treatment in 36/75 patients (48%) on one or more occasions, only one of them having had a raised platelet count (496,000/μl) beforehand. The characteristics of the patients in relation to whether or not they developed thrombocytosis are shown in Table 1. There is a tendency for patients with thrombocytosis to have more advanced tumours at diagnosis but otherwise their characteristics are similar. The maximum platelet counts observed are shown in Table 2 and it is seen that the phenomenon of thrombocytosis was more common in the 35 patients receiving concomitant progestogen therapy (25/35 = 71.4%) compared with 40 patients not so treated (11/40 = 27.5%); $\chi^2 = 12.73$, $P < 0.001$. Furthermore, thrombocytosis was observed on more occasions (Table 3) and lasted longer (Table 4) in patients treated with the progestogen.

*Leukopenia (total white cell count below* 4000/μl)

This condition occurred in only 5/36 patients who developed thrombocytosis compared with 24/39 in those who did not ($\chi^2$

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*Present address: Department of Medical Oncology, Charing Cross Hospital, London W6 9RF, United Kingdom.
†To whom correspondence should be addressed.

*Table 1. Characteristics of patients*

| Medical history | (No. of Patients) With thrombocytosis ($n=36$) | Without thrombocytosis ($n=39$) |
|---|---|---|
| (1) Disease-free interval | | |
| 0–2 yr | 29 | 28 |
| >2 yr | 7 | 11 |
| (2) Stage at first diagnosis | | |
| Operable (I, II) | 15 | 28 |
| Primarily advanced (III, IV) | 21 | 11 |
| (3) Previous treatment for advanced disease | | |
| Ovarian ablation | 14 | 10 |
| Androgens | 8 | 16 |
| Oestrogens | 14 | 14 |
| Hypophysectomy | 10 | 13 |
| Prednisone | 7 | 6 |
| Radiotherapy | 33 | 36 |
| | (Years) With thrombocytosis | Without thrombocytosis |
| (1) Age | | |
| Mean | 50.0 | 50.0 |
| Radian | 49.5 | 50.0 |
| Range | 27–69 | 29–77 |
| (2) Time from diagnosis to start of treatment with chemotherapy | | |
| Mean | 3.8 | 4.4 |
| Median | 3.0 | 3.0 |
| Range | 0–15 | 0–15 |

*Table 2. Maximum platelet counts recorded in 36 patients with thrombocytosis*

| Maximum platelet count $\times 10^5$ | Treated with progestogen ($n=35$) | Treated without progestogen ($n=40$) |
|---|---|---|
| $\geqq 4-<5$ | 9 | 6 |
| $\geqq 5-<6$ | 8 | 0 |
| $\geqq 6-<8$ | 4 | 5 |
| $\geqq 8$ | 4 | 0 |
| Total | 25 | 11 |

*Table 3. Number of occasions on which thrombocytosis was observed in 36 patients with thrombocytosis*

| Number of occasions thrombocytosis noted | Treated with progestogen ($n=35$) | Treated without progestogen ($n=40$) |
|---|---|---|
| 1 | 4 | 5 |
| 2 | 8 | 4 |
| 3 | 3 | 0 |
| 5 | 1 | 1 |
| 6 | 4 | 1 |
| 7 | 3 | 0 |
| 9 | 2 | 0 |
| Total | 25 | 11 |

*Table 4. Duration of thrombocytosis*

| Duration of longest period of thrombocytosis (weeks) | Treated with progestogen ($n=35$) | Treated without progestogen ($n=40$) |
|---|---|---|
| <4 | 11 | 10 |
| 4–<8 | 7 | 0 |
| 8–<12 | 1 | 1 |
| 12–<16 | 4 | 0 |
| 16–<20 | 1 | 0 |
| 20–<24 | 1 | 0 |
| Total | 25 | 11 |

$=17.92$, $P<0.001$). In relation to progestogen therapy leukopenia occurred in 8/35 patients so treated and in 21/40 patients not given concomitant norethisterone acetate.

*Neurotoxicity*

Forty-eight patients developed clinical features of neurotoxicity while on treatment with vincristine and in 17 this necessitated stopping the drug. Twenty-seven of these 48 patients had thrombocytosis and in relation to progestogen therapy 26 of the 48 received progestogen. Twenty of the patients with neurotoxicity received progestogen and also had thrombocytosis.

*Thrombo-embolism*

Eight patients developed thrombo-embolic disease (Table 5). Some of the cases could be attributable to co-existing disease, as in the case of a patient with a probable adriamycin-induced cardiomyopathy who had a cerebral embolus. Diabetes mellitus and ischaemic heart disease could have predisposed to thrombo-embolism in 2 patients. The mean of the recorded platelet counts of 5 of these patients who had elevated platelet counts was 461,000/$\mu$l and, in the 3 patients who did not have thromocytosis, the mean platelet count was 215,000/$\mu$l.

*Response to treatment*

Seventy patients were assessable [6], 35 of whom had thrombocytosis and 35 did not. Twenty-three of the patients with thrombocytosis had an objective regression [6], but only 13/35 without thrombocytosis showed such a response to treatment ($\chi^2=5.7$; $P<0.02$). The addition of a progestogen to chemotherapy *per se* did not lead to an improved response rate [4]. In this study, 14 of the responding patients with thrombocytosis received progestogen (14/23) and in those who did not respond. 10/12 received progestogen. One patient without thrombocytosis who received progestogen had an objective regression (1/13) and nine patients without thrombocytosis who did not respond received progestogen (9/22). It appeared therefore that those patients who did not have thrombocytosis and were treated with concomitant progestogen had the least chance of an objective regression.

*Cytotoxic drug administration*

Patients developing thrombocytosis had less dose reductions of adriamycin, receiving 87% of the calculated full dose compared with 82% for the patients without thrombocytosis, but this difference is not significant ($P<0.1$).

## DISCUSSION

This study has demonstrated a 48% incidence of thrombocytosis in patients receiving vincristine in combination with the myelosuppressive drug adriamycin, this occurrence being significantly more common when a progestogen was given concomitantly. Thrombocytosis observed in this study may not be due invariably to vincristine, as in some cases it may simply be a feature of underlying malignancy [7]. The occurrence of thrombocytosis was associated with a significantly better therapeutic response to chemotherapy, but the reason for this is obscure. While it may be postulated that vincristine could protect bone marrow from the myelosuppressive effects of other cytotoxic drugs allowing a higher more effective dose to be given, this was not demonstrated to be the case in this study.

The mechanism of vincristine-induced thrombocytosis is uncertain. It may result from

*Table 5. Thrombo-embolic complications in 8 patients, in relation to the occurrence of thrombocytosis and concomitant administration of norethisterone acetate*

| Patient | Thrombo-embolic complication | Occurrence of thrombocytosis | Concomitant norethisterone acetate administration |
|---|---|---|---|
| 1 | Cerebral embolus | yes | yes |
| 2 | Pulmonary embolus | yes | yes |
| 3 | Pulmonary embolus | yes | no |
| 4 | Deep vein thrombosis | yes | yes |
| 5 | Pulmonary embolus | yes | yes |
| 6 | Deep vein thrombosis Pulmonary embolus | no | no |
| 7 | Pulmonary embolus | no | yes |
| 8 | Superficial thrombosis | no | no |

a direct increase in platelet production from megakaryocytes [2], but immunosuppression has been suggested as the reason for improvement in platelet counts in idiopathic thrombocytopenia [8]. A further possibility is that vincristine may stimulate megakaryocytopoiesis by altering a functional role of platelets in the regulation of thrombopoiesis. Since vincristine at high doses damages platelets and shortens platelet survival, low-dose vincristine may alter circulating platelets in such a way that they are no longer recognised by the thrombopoietic regulatory system, with a consequent increase in platelet production [9].

Patients with cancer probably have a predisposition to thromboembolic disease. The association between venous thrombosis and cancer was described more than 100 yr ago by Trusseau [10] and has been reported upon in literature since [7]. Furthermore, in the presence of an elevated platelet count it might be expected to occur more frequently. However, in this study, neither thrombocytosis nor the addition of a progestogen appeared to predispose to thrombo-embolic complications. It has been shown here that vincristine-induced thrombocytosis, which is augmented by norethisterone acetate, correlates with a better response to chemotherapy, yet the progestogen itself does not contribute to the therapeutic efficacy of treatment [4]. It must, therefore, be speculated that the progestogen has at least two different activities; first, potentiation of the thrombocytosis, and, secondly, a direct effect on the tumour. If this latter action leads to suppression of tumour cell proliferation, then cytotoxic drug action may be antagonised [4]. Presumably, it is the balance between these two factors which determines the influence of thrombocytosis and progestogen therapy in leading to tumour regression. Conceivably, the presence of progestogen receptors [11] could be of importance in this regard, but this information was not available on many of the patients in this study. At the present time, it is not possible to make recommendations about the relevance of the phenomenon of augmentation of vincristine-induced thrombocytosis in the selection of treatment for patients with advanced breast cancer.

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## REFERENCES

1. P. P. Carbone, V. Bono and C. O. Bindley, Clinical studies with vincristine. *Blood* **21,** 640 (1963).
2. J. H. Robertson, E. H. Crozier and B. E. Woodend, The effect of vincristine on the platelet count in rats. *Brit. J. Haemat.* **19,** 331 (1970).
3. P. Barkhan, Today's treatment: blood and neoplastic diseases; thrombocytopenia. *Brit. med. J.* **2,** 324 (1974).

4. R. D. RUBENS, R. H. J. BEGENT, R. K. KNIGHT, S. A. SEXTON and J. L. HAYWARD, Combined cytotoxic and progestogen therapy for advanced breast cancer. *Cancer (Philad.)* **42,** 1680 (1978).
5. R. D. J. EASTHAM, Technical methods: rapid whole-blood platelet counting using an electronic particle counter. *J. clin. Path.* **16,** 168 (1963).
6. J. L. HAYWARD, P. P. CARBONE, J.-C. HEUSON, S. KUMAOKA, A. SEGALOFF and R. D. RUBENS, Assessment of response to therapy in advanced breast cancer. *Europ. J. Cancer* **13,** 89 (1977).
7. R. B. DAVIES, A. THEOLOGIDES and B. J. KENNEDY, Comparative studies of blood coagulation and platelet aggregation in patients with cancer and non-malignant diseases. *Ann. intern. Med.* **71,** 67 (1969).
8. Y. S. ANN, W. J. HARRINGTON, R. C. SLEETMAN and C. S. ETHEL, Vincristine therapy of idiopathic and secondary thrombocytopenias. *New Engl. J. Med.* **291,** 376 (1974).
9. C. W. JACKSON, C. C. EDWARD, Evidence that stimulation of megakaryocytopoiesis by low dose vincristine results from an effect on plateless. *Brit. J. Haemat.* **36,** 97 (1977).
10. A. TRUSSEAU, Phlegmasia Alba Dolens. Clinique Médicale de l'Hôtel-Dieu de Paris. Vol. III. 2nd Edn., Baillière, Paris (1865).
11. K. B. HORWITZ, W. L. MCGUIRE, O. H. PEARSON and A. SEGALOFF, Predicting response to endocrine therapy in human breast cancer: a hypothesis. *Science* **189,** 726 (1975).