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VP 16–213 in acute myelogenous leukaemia

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Summary

The use of the epipodophyllotoxin VP 16–213 is described in twenty patients with acute myelogenous leukaemia resistant to other chemotherapy. The drug was usually given in 5-day courses of 50 mg/m² daily and occasionally in 24-hr infusions of 250 mg/m², on the basis of its phase-activity.

Complete remission was achieved in only two patients: in one of these, remission was maintained with VP 16–213 for 8 months, and in the other for 10 weeks. A partial response was achieved in one other patient. Seventeen patients showed no response. No responses or remissions were achieved when the drug was used in a 24-hr infusion. Side effects were minimal, and the degree of marrow depression much less than for most other agents known to be active in acute myelogenous leukaemia. It was of interest that remission was achieved in one patient without the customary period of marrow hypoplasia. It is suggested that, although VP 16–213 appears to have minimal activity in the dosage used here, improvement might be sought by increasing the dosage, by scheduling the drug in a different way, or by using it in a combination chemotherapy regime.

Introduction

VP 16–213 (Sandoz), a semi-synthetic derivative of the plant product podophyllotoxin, is a cytotoxic drug which a preliminary study has suggested might be active in some human malignancies including acute monocytic and myelomonocytic leukaemia (E.O.R.T.C., 1973).

In a study of VP 16–213 by the European Organisation for Research on Treatment of Cancer, the drug was given daily for a 5-day period. Like V.M. 26, (Stähelin, 1970), it is a phase-active compound, preventing cells from entering mitosis or killing them in pre-mitosis (Dombernowsky and Nissen, 1973). This suggested that greater leukaemic cell kill with relative marrow sparing might be achieved by high dose infusions over a short period, as demonstrated experimentally for other cytotoxic agents (Bruce, Meeker and Valeriote, 1966), and later applied clinically with methotrexate (Goldie, Price and Harrap, 1972). This hypothesis is supported by experimental data in which VP 16–213 was more effective against the mouse L 1210 leukaemia when given in divided doses over a 24-hr period, than in single daily doses (Dombernowsky and Nissen, 1973). This prompted the authors to use VP 16–213 as a high dose 24-hr infusion in some of their patients.

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Patients and methods

VP 16–213 was given to twenty patients with acute myelogenous leukaemia; sixteen of these had acute myeloblastic leukaemia, three acute myelomonocytic, and one acute undifferentiated leukaemia. All were in relapse, either from the time of initial presentation or after a period of remission, and all had failed to respond to conventional therapy with various combinations of cytosine arabinoside, daunorubicin, adriamycin and 6-thioguanine (Table 1).

VP 16–213 was given to eighteen of the patients in an i.v. injection of 50 mg/m² daily for 5 days. This was repeated at two-weekly intervals until it became obvious that the disease was continuing to progress, which in many patients was apparent after only one course. The drug is presented as a viscous water soluble fluid in 10 ml ampoules and because of the high viscosity of the drug it was necessary to dilute it to 50 ml with normal saline for ease of administration.

In four patients, VP 16–213 was given in a 24-hr infusion in a dose of 200–250 mg/m² (i.e. the total 5-day dosage) and, in all, seven 24-hr infusions were given to these four patients (Table 2). Initially, problems arose with drug precipitation when doses of 250 mg/m² (total dose 300–500 mg) were dissolved in one litre of either normal saline or 5% dextrose.

TABLE 1.

No.	Age/sex	Diagnosis	Previous treatment	VP 16–213 dose	Result	Complications	Marrow depression
1	65 M	A.M.L.	Ara-C, 6-TG, cyclophosphamide	(a) 50 mg/m² × 5 days 3 courses at 2 week intervals between each course	(a) *Partial response* Marrow 45%→5% blasts after 2 courses, then deterioration	(a) Alopecia	Neutrophils ↓ (900 → 300) with rapid recovery
				(b) 300 mg, 24-hr infusion	(b) No response	(b) Nil	Neutrophils ↓ (2000 → 300) after 3rd course
2	64 M	A.M.L.	Ara-C and daunorubicin partial response then relapse	50 mg/m² × days 15 courses at 2 week intervals between each course	*Complete remission* 8 months then skin relapse 11 months then marrow relapse	Transient nausea in later courses	After 1st course Platelets ↓ (95,000 → 20,000) Since then no depression of normal blood count
3	62 F	A.M.L.	Ara-C	50 mg/m² × 5 days 1 course	No response	Nil	None
4	49 M	A.M.M.L.	Ara-C, daunorubicin, 6-TG	50 mg/m² × 5 days 1 course	No response	Nil	None
5	53 M	A.M.L. (2nd relapse)	Ara-C, daunorubicin, adriamycin	50 mg/m² × 5 days 1 course	No response	Transient nausea	None
6	27 M	A.M.L. (1st relapse)	Ara-C, daunorubicin	50 mg/m² × 5 days 1 course	No response	Transient nausea	None
7	34 F	A.U.L.	Ara-C, daunorubicin	250 mg/m² 24-hr infusion 1 course	No response	Pretreatment viral pneumonia became more severe	Very marked depression of all marrow elements without differential leukaemic cell kill
8	21 M	A.M.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin	250 mg/m² 24-hr infusion 2 courses at 1 wk interval	No response	Vomiting during infusion	Not assessable: hypocellular throughout
9	58 F	A.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin, 6-TG	50 mg/m² × 5 days 1 course	No response	Nil	Platelets ↓ (40,000 → 8000)

A.M.L., acute myeloblastic leukaemia; A.M.M.L., acute myelomonocytic leukaemia; A.U.L., acute undifferentiated leukaemia.

continued overleaf

TABLE 1. *continued*

No.	Age/sex	Diagnosis	Previous treatment	VP 16–213 dose	Result	Complications	Marrow depression
10	55 F	A.M.L.	Ara-C, 6-TG	50 mg/m² × 5 days 1 course	No response	Nil	Neutrophils ↓ (3000 → 300)
11	67 M	A.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin, 6-TG, persistent 30% marrow leukaemic blasts	50 mg/m² × 5 days 6 courses at 2 wk intervals between each course	*Complete remission* after 1 course 10 weeks duration	Superficial thrombophlebitis left leg 10 days after 1st course	Neutrophils ↓ (600 → 200) after 1st course, then ↓ Platelets
12	48 F	A.M.L.	Ara-C, daunorubicin, adriamycin, 6-TG	(a) 50 mg/m² × 5 days 1 course (b) 250 mg/m² 24-hr infusion 1 course	(a) No response (b) No response	(a) Nil (b) nil	Not assessable: hypocellular throughout
13	50 M	A.M.L.	Ara-C, adriamycin, 6-TG, 6-M.P., cyclophosphamide, prednisolone	50 mg/m² × 5 days	No response	Worsening of pre-treatment septicaemia	Not assessable: hypocellular throughout
14	49 F	A.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin 6-TG	50 mg/m² × 5 days 2 courses at 2 wk intervals	No response	Nil	Neutrophils ↑ after 1st course Neutrophils ↓ (900 → 200 after 2nd) Platelets ↓ after 2nd course (70,000 → 20,000)
15	23 M	A.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin	50 mg/m² × 5 days 1 course	No response	Nil	Nil
16	67 F	A.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin, 6-TG, cyclophosphamide	50 mg/m² × 5 days 1 course	No response	Nil	Neutrophils ↓ (6000 → 2000)
17	35 F	A.M.L.	Ara-C, daunorubicin, 6-TG, adriamycin	50 mg/m² × 5 days 1 course	No response	Nil	Neutrophils ↓ (2300 → 1000)
18	43 F	A.M.L. (1st relapse)	Ara-C, daunorubicin, adriamycin, 6-TG	50 mg/m² × 5 days 1 course	No response	Nil	Neutrophils
19	66 F	A.M.M.L.	Ara-C, daunorubicin, adriamycin, 6-TG	50 mg/m² × 5 days 1 course	No response	Nil	Nil
20	60 M	A.M.M.L.	Ara-C, daunorubicin adriamycin, 6-TG	50 mg/m² × 5 days 1 course	No response	Nil	Not assessable hypocellular throughout

A.M.L, acute myeloblastic leukaemia; A.M.M.L., acute myelomonocytic leukaemia; A.U.L., acute undifferentiated leukaemia.

TABLE 2. Side effects and toxicity of VP 16-213

	Daily × 5 days	24-Hour infusion
Infection	1 Septicaemia	1 Pneumonia/exacerbation
Neutrophil depression	7/18	1/7
Platelet depression	3/18	1/7
Nausea	5/18	1/7
Vomiting	—	1/7
Alopecia	1/18	—
Thrombophlebitis	1/18	—
Stomatitis, oral ulceration, gastro-intestinal upset	—	—

This was overcome by increasing the dilution to 3 l of 5% dextrose, infusing each litre eight-hourly over 24 hr.

Peripheral blood counts, plasma urea, electrolytes and protein, serum liver enzymes and bilirubin were monitored before and after treatment. Bone marrow aspirates were done before and after each course of treatment.

Full supportive therapy during treatment, including blood and platelet transfusions and antibiotics where appropriate, was given to all patients.

Results

Two patients with acute myeloblastic leukaemia achieved complete haematological and clinical remission after treatment with VP 16–213. The first of these (Case 2, Table 1), achieved remission after one 5-day course of therapy, without depression of peripheral blood count. He was maintained in remission on 5-day courses at two-weekly intervals for 9 months before developing leukaemic skin infiltrates. He subsequently developed marrow relapse 11 months after the start of VP 16–213 therapy. His presenting marrow aspirate showed basophilic plasmocytoid blast cells with a low nuclear/cytoplasmic ratio and unusual appearance, but three haematologists independently confirmed a morphological diagnosis of acute myeloblastic leukaemia. No side effects were experienced from courses of maintenance treatment given at 2-weekly intervals for 9 months, except for occasional transient nausea on the first and second day of each course.

The second patient (Case 12, Table 1), also achieved remission after one 5-day course of therapy, with depression of blood neutrophils but not of platelets. He was maintained in remission on 5-day courses at 2-weekly intervals for 10 weeks before haematological relapse.

One patient (Case 1, Table 1) with acute myeloblastic leukaemia showed a partial response to VP 16–213. His marrow aspirate showed a fall in leukaemic blasts from 50 to 7% with rising peripheral platelet count after two courses of treatment, but the effect was short-lived and the marrow once more deteriorated after the third course of treatment.

None of the remaining seventeen patients showed any response to VP 16–213 therapy and in particular no response was seen to any of the seven 24-hr infusions.

In general, treatment was well tolerated with a remarkably low incidence of toxicity (Table 2). Bone marrow depression due to VP 16–213 was rarely severe, although many patients had severely hypoplastic bone marrows before therapy, because of disease and previous treatment. A fall in neutrophil count was seen in eight patients and a fall in platelet count in four; on the other hand, the neutrophil count rose in four instances after therapy, and the platelets rose in two. It was often hard to interpret whether these results were directly attributable to VP 16–213 or to prolonged effects of previous therapy.

Nausea occurred transiently in five patients but was associated with vomiting in only one, and this was during a 24-hr infusion. Other gastro-intestinal disturbances, including oral ulceration, were not seen. Reversible alopecia occurred in one man. No disturbance in plasma electrolytes, urea, serum liver enzymes or bilirubin attributable to VP 16–213 was seen.

Discussion

This study suggests that VP 16–213 is only rarely effective in the treatment of acute myelogenous leukaemia, as a single agent given either as a course of five daily injections or in a single high dose infusion over 24 hr. It was also not possible to confirm in the three patients with acute myelomonocytic leukaemia the E.O.R.T.C. (1973) finding that the drug is particularly effective in this type of leukaemia. Nevertheless, the complete remission obtained in one patient (Case 2, Table 1) was striking in that it was achieved without a significant degree of marrow suppression at any stage. This is very unusual with other current chemotherapy effective against acute myelogenous leukaemia. It was of interest that this patient had a morphologically unusual myeloblastic leukaemia.

In the dosage described, VP 16–213 rarely produced severe marrow toxicity or unpleasant side

effects, in contrast to most other anti-leukaemic agents. This, despite its low remission rate, perhaps justifies the continuing use of the drug as a last resort, in that at least it is unlikely to worsen the patient's condition.

There are possible ways in which the effectiveness of VP 16–213 might be improved. Firstly, the relatively moderate bone marrow toxicity suggests that the dose of the drug might be increased without life-threatening consequences, particularly if it were given as first line treatment, without a marrow made hypoplastic by previous chemotherapy. Secondly, its phase-activity and increased efficiency with scheduling in the L 1210 experimental leukaemia (Dombernowsky and Nissen, 1973) suggests that appropriate scheduling might produce better clinical effect, despite the lack of response to a 24-hr infusion in the authors' experience. Finally, VP 16–213 might be more effective used in combination or sequential chemotherapy.

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