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# Continuous vincristine infusion as part of a high dose chemoradiotherapy regimen: drug kinetics and toxicity

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**Summary.** A 5-day continuous infusion of vincristine (VCR; total dose 4 mg/m$^2$) has been given as part of a high-dose chemoradiotherapy regimen with bone marrow transplantation. Evidence of neurotoxicity, such as weakness, paraesthesia and intestinal hypomotility, was evaluated prospectively in nine patients. Five patients had advanced neuroblastoma and four, relapsed sarcomas, and all had responded to initial conventional-dose therapy. VCR was combined with high-dose melphalan (180 mg/m$^2$) and fractionated total-body irradiation. Plasma concentrations of VCR were measured by radioimmunoassay during and up to 24 h after the infusion. Serum and urine electrolytes and liver function tests were measured during VCR treatment and at regular intervals thereafter. VCR concentration at 1 h ranged from 1.8 to 10.9 (median 6.6) ng/ml, and a steady state was achieved by 13–30 h (median 16 h). Levels above 1 ng/ml were maintained throughout the 5-day period with a mean steady-state concentration of 1.7 ng/ml (range 1.3–2.15). After cessation of the infusion, serum concentrations fell to below 0.25 ng/ml within 24 h. Abdominal pain occurred in one patient, but neither constipation nor ileus was seen. In two patients severe muscle pain occurred in the lower limbs towards the end of the infusion. Significant electrolyte problems did not occur and, in particular, there was no evidence of inappropriate ADH secretion. Transient increases in liver enzymes were common but bilirubin was not elevated during the period of monitoring. This regimen allows a two-fold escalation in the dose of VCR to be administered, producing sustained high serum drug levels without major toxicity.

## Introduction

Vincristine (VCR) plays an important role in the management of solid and haematological tumours in infancy. Its broad spectrum of activity and lack of myelosuppression have led to its incorporation in many standard schedules. The main dose-limiting toxicity involves the nervous system, in the form of either peripheral neuropathy or hypomotility of the small intestine. These have limited the dose of single bolus treatments to a maximum of 2 mg/m$^2$ given weekly for up to several weeks and then monthly. Dose or schedule alteration are not uncommon, however, owing to the development of foot drop, weakness, abdominal pain or even ileus. Other less commonly reported side effects include liver function derangement and inappropriate ADH secretion.

The importance of drug scheduling has been long recognised, but has recently been given emphasis since the lack of new effective anticancer agents has stimulated attempts to optimise the use of existing drugs. Alterations in scheduling usually involve the change from a single bolus dose to either multiple divided doses or infusion over several days. With some drugs there are theoretical reasons for predicting that such scheduling would be more effective, for example, if the mechanism for production of active metabolite was rapidly saturated with high single doses. It has also been suggested that prolonged exposure of tumour cells to chemotherapy may be more cytotoxic, as it would influence cells passing through cell cycle over this period. This might apply to highly phase-specific agents, such as the vinca alkaloids, which are most active on cells during M phase. Moreover, with some agents a divided dose schedule appears to be less toxic to normal tissues (e.g., cisplatin, ifosfamide) and allows a higher total dose to be administered.

In the case of VCR this approach has been applied in adults with a variety of solid tumours. Phase I studies have shown that up to 0.5 mg/m$^2$ can be given for 5 days without major toxicity [8]. Although there have been reports of responses in patients who have relapsed after regimens including conventional-dose VCR, there is no clear evidence of superior activity in untreated patients given VCR by infusion. Experience in paediatric practice is limited [4, 15].

Radioimmunoassay studies in adults have demonstrated considerably higher areas under the concentration curve (AUC) when VCR is given in this way [9]. In an attempt to improve outcome in neuroblastoma and high-risk or relapsed sarcomas, high-dose chemoradiotherapy procedures have been introduced in many centres [16]. High-dose melphalan and total-body irradiation is a combination that is widely used for a variety of tumours and leukaemias. The purpose of adding VCR to this combination was to try and escalate the dose of this active drug and also possibly recruit cells into cycle prior to high-dose melphalan.

## Patients and methods

Nine patients aged 2–25 (median 7) years were treated with high-dose chemoradiotherapy for consolidation of first or second remission of either neuroblastoma [14] or

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**Table 1.** Clinical details of patients, prior therapy and toxicity related to vincristine infusion

| Patient | Age (years) | Diagnosis | Previous chemotherapy | Toxicity with VCR infusion (WHO grade) |
|---|---|---|---|---|
| 1 | 6 | Relapsed neuroblastoma | PE-CADO HD CDDP-VP16 | Leg pain (2) |
| 2 | 15 | Relapsed rhabdomyosarcoma | IVA Adr-CDDP | Abdominal pain (2) |
| 3 | 25 | Relapsed sarcoma | IVA Adr-CDDP | |
| 4 | 2 | Neuroblastoma | HD CDDP-VP16 | |
| 5 | 2 | Neuroblastoma | HD CDDP-VP16 | |
| 6 | 15 | Ewing's sarcoma | IVAAd | Leg pain (2) |
| 7 | 19 | Esthesioneuroblastoma | PE-CADO | Leg pain (2) |
| 8 | 3 | Neuroblastoma | PE-CADO | |
| 9 | 7 | Neuroblastoma | PE-CADO HD CDDP-VP16 | |

PE-CADO, Cisplatin, etoposide, cyclophosphamide, adriamycin, vincristine; HD CDDP-VP16, high-dose platinum, etoposide; IVAAd, ifosfamide, vincristine, actinomycin, adriamycin; Adr-CDDP, adriamycin, cisplatin

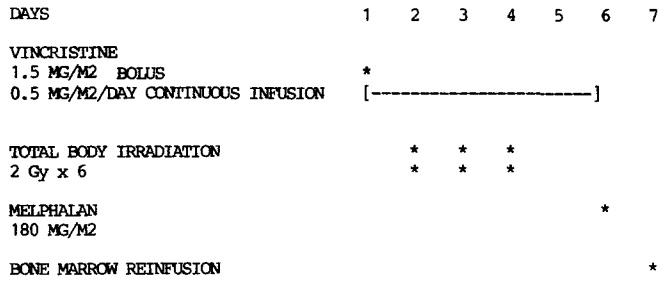


**Fig. 1.** Outline of vincristine infusion regimen preceding high-dose melphalan, total-body irradiation and bone marrow transplant

sarcoma [16]. Previous chemotherapy included vincristine, adriamycin, cyclophosphamide, ifosfamide, cisplatin, and etoposide (Table 1). The high-dose regimen is summarised in Fig. 1. Fractionated total-body irradiation was preceded by high-dose melphalan and the infusion of vincristine. Autologous bone marrow was reinfused 24 h after melphalan. The vincristine infusion commenced with a single bolus dose (1.5 mg/m$^2$) followed by 0.5 mg/m$^2$ per day infused through a central venous catheter over 5 days as previously reported [1, 15].

*Clinical evaluation.* Patients were examined and questioned daily with specific regard to abdominal or muscle pain, jaw pain, numbness, tingling or paraesthesia. Bowel activity was noted. Daily biochemical monitoring included plasma sodium, potassium, chloride, bicarbonate, urea, creatinine, liver transaminases, gamma GT, and alkaline phosphatase. Urine electrolytes were estimated on at least two occasions during the VCR infusion.

*Drug level assay.* VCR plasma concentrations were estimated according to a modification of the radioimmunoassay described by Teale [17]. $^3$H-Vinblastine (10.7 Ci/mmol, Radiochemical Centre, Amersham, Bucks.) was used as a tracer and the antisera were used at an initial dilution of 1:1000, when approximately 50% of the added tracer was bound by the antisera in the absence of unlabelled alkaloid. Both vinblastine and vincristine displaced antisera bound $^3$H-vinblastine. Non-specific binding of tracer to normal plasma was less than 6%. Clinical grade VCR sulphate, 99% (Sigma Chemicals) was used to prepare appropriate standards. The limits of sensitivity of the assay were 250 pg VCR per ml plasma, and intra- and interassay variation was less than 4% and 9% respectively. Samples were drawn from the central venous catheter after rigorous flushing with normal saline. Because of the age of the patients we felt it was not justified to insert additional peripheral venous canulas specifically for study purposes. Samples were taken prior to the bolus dose of VCR and approximately three times per day during the 5-day infusion and the 48 h following cessation of the infusion. Plasma was separated by centrifugation and stored at −20° C until analysis.

## Results

### *Clinical studies*

The results of biochemical monitoring are shown in Table 2. There was a clear upward trend in liver function tests – transaminases, gamma GT and LDH. The enzymes rarely exceeded the normal range, however, and in several cases the LDH was already high as a consequence of prior chemotherapy. Serum bilirubin was not elevated in any patient. Serial plasma electrolyte assay showed a downward trend for sodium, potassium and chloride although again the normal range was not exceeded. Plasma urea and creatinine remained normal.

There was no occurrence of clinically significant inappropriate ADH excretion that required therapeutic intervention.

The most marked clinical toxicity was limb and jaw pain, which occurred in three patients starting at days 3–5 of the infusion. In all cases this was severe enough to need systemic opiate analgesia and lasted for up to 5 days. Severe abdominal pain occurred in one patient, but there was no clinical evidence of ileus. Observations of toxicity were not extended beyond day 10 because of the superimposition of toxicity related to melphalan and total-body irradiation.

**Table 2.** Biochemical data during vincristine infusion and up to 10 days thereafter. Pretreatment and maximum change in values are shown

| Patient | Liver function | | | | Plasma | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | γGT | ALT | AST | LDH | Urea | Creatinine | Sodium (mmol/l) | Potassium | Chloride | Bicarbonate |
| | I. u./l | | | | | | | | | |
| 1 | 25–56 | 30– 38 | 40– 65 | 690– 952 | 7–3.5 | 41–56 | 133–131 | 3.9–2.8 | 101– 92 | 23–17 |
| 2 | 37–61 | 35– 12 | 37– 41 | 518– 711 | 3.8–3.8 | 69–64 | 136–132 | 3.5–3.0 | 106– 97 | 23–28 |
| 3 | 30–47 | 34– 98 | 34– 62 | 453– 605 | 4–2.1 | 81–66 | 141–143 | 4.0–2.9 | 106– 99 | 25–22 |
| 4 | 15–25 | 20– 27 | 37– 49 | 611– 812 | 5.6–2 | 38–21 | 140–134 | 3.7–2.9 | 106– 98 | 21–33 |
| 5 | 10–34 | 19– 47 | 36– 44 | 749– 623 | 1.7–4.6 | 19–34 | 139–127 | 4.3–2.8 | 104–109 | 24–42 |
| 6 | 33–47 | 19– 36 | 29– 43 | 488– 627 | 2.3–2.7 | 62–55 | 143–129 | 3.6–2.8 | 108–103 | 23–18 |
| 7 | 15–36 | 13– 42 | 17– 36 | 432– 574 | – | 80–71 | 144–145 | 4.1–3.2 | 105–103 | 24–31 |
| 8 | 22–38 | 34–100 | 53–125 | 819–1321 | 5.6–4.7 | 37–75 | 140–136 | 3.7–4.4 | 106– 97 | 25–23 |
| 9 | 72–69 | 109– 38 | 132– 58 | 869– 660 | 417–2.3 | – | 136–136 | 3.5–2.8 | 100– 98 | 26–25 |

**Table 3.** Pharmacokinetics parameters of vincristine disposition during 5-day infusion

| Patient | Concentration at 1 h (ng/ml) | Time to reach steady state (h) | Mean state steady concentration (ng/ml) | Total-body clearance[a] (l/kg per h) |
|---|---|---|---|---|
| 1 | 9.8 | 16 | 1.56 | 0.67 |
| 2 | 6.6 | 21 | 1.62 | 0.38 |
| 3 | – | – | 2.04 | 0.32 |
| 4 | 10.9 | 14 | 2.15 | 0.44 |
| 5 | – | – | 1.42 | 0.70 |
| 6 | 6.1 | 30 | 1.29 | 0.67 |
| 7 | 7.1 | 13 | 1.97 | 0.13 |
| 8 | 4.9 | 19 | 1.66 | 0.55 |
| 9 | 1.8 | 15 | 1.38 | 0.74 |

[a] Total-body clearance was calculated as rate of infusion/mean steady-state concentration

*Plasma drug profiles*

Details of plasma VCR concentrations are shown in Table 3. In general a steady state was rapidly achieved and a minimum drug concentration between 1 and 5 ng/ml was maintained throughout the infusion period. There were, however, unexplained peaks up to between 20 and 50 ng/ml in three patients. The cause of these is not clear. Central line samples were taken in a consistent manner with adequate flushing on each occasion and there is no reason to believe the infusion pump rates were altered at any time. It is possible that these were associated with times when the infusion pump changed, when additional drug may have been inadvertently injected as a bolus. During the infusions median plasma VCR levels were 1.3, 1.8, 2.7, 2.5, 1.4, 1.3, 1.7, 1.7, 1.1 ng/ml.

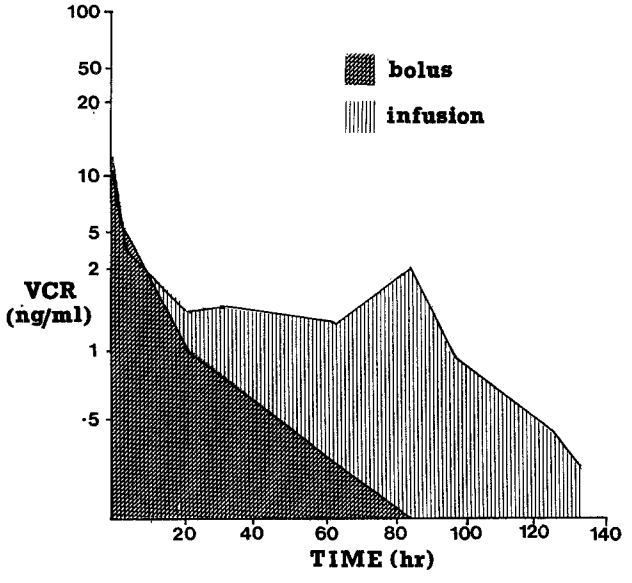


**Fig. 2.** Typical serum VCR profile during 5-day infusion (patient 9) contrasted with that after a single bolus dose of 1 mg/m$^2$. (Adapted from [18])

The profile of one patient (no. 9) is shown in Fig. 2, contrasted with that described after a single bolus dose of 1 mg/m$^2$ [18].

Following cessation of the infusion, drug concentrations fell rapidly, but the number of samples taken during this period was insufficient for accurate calculation of drug half-life. One-hour drug concentration, steady-state concentration, and total-body clearance are shown in Table 3.

## Discussion

As was anticipated from previous studies in adults, this method of drug administration enabled more than a two-fold escalation in the dose of VCR. Single bolus doses of greater than 2 mg/m$^2$ are rarely administered and have been associated with severe toxicity when given inadvertently. Two or three times the normal dose has been reported to cause marked paraesthesia, bone pain, paralytic ileus, severe inappropriate ADH (antidiuretic hormone) syndrome and grand mal seizures [12, 13]. The most nota-

ble toxicity in our patients was muscle pain occurring towards the end of infusion. This type of deep, boring pain, occurring in any part of the axial or appendicular skeleton or as severe maxillary, mandibular or throat pain, was clearly described in early dose escalation studies in adults using weekly administration [5] and was a prominent feature in both phase I studies of the 5-day infusion [8] and subsequent clinical studies with this regimen [1, 11, 15, 18]. In contrast, the incidence of severe abdominal pain was lower than expected. This may be age-related, as abdominal symptoms were noted in 9/16 patients in a previous series in which the median age was 45 years, as against 7 years in the present study [1]. Peripheral neurotoxicity was not a problem. Most of these patients had received conventional-dose VCR prior to the autograft procedure, and ankle jerk reflexes were therefore rarely present. Despite this, in no patient did the toxic effects progress to significant persistent paraesthesia or motor problems. The effect of prior exposure to VCR cannot be determined from this study but may be a contributory factor. Only two patients had not received VCR and neither of these developed acute toxicity. The results were recorded after only a single course of VCR infusion, and it is likely that toxicity would be much more marked if repeated courses were given [1].

Pharmacokinetic information from these data are limited but they confirm a relatively steady state beyond 18 h during the infusion period, with plasma drug levels in excess of 1 ng/ml. Studies in children with acute leukaemia have demonstrated that after a single bolus dose of 1 mg/m$^2$, VCR levels decline from 10 ng/ml at 1 h to less than 1 ng at 24 h, with an elimination half-life of 8.2 h [18]. In adults an infusion of 0.5 mg/m$^2$ per day for 5 days achieved serum VCR concentration of $0.2-1.3 \times 10^{-8}$ *M* of 24–120 h and this was not significantly greater at a dose of 1 mg/m$^2$ per day [9].

A correlation between cytotoxicity and duration of drug exposure has been demonstrated in the L1210 murine leukaemia cell line [7], but in rhabdomyosarcoma xenograft studies antitumour effect was related to selective drug retention [6]. In the absence of any comparative studies, it is impossible to make any conclusion on the relative efficacy of administration schedules. In the present study, most patients had little or no measurable disease, so no attempt to correlate kinetic parameters with response can be made.

A correlation between liver function, VCR clearance and neurotoxicity has been demonstrated in children with leukaemia [2]. Acute hepatotoxicity has also been documented but is usually self-limiting [3, 19]. In the present study there was evidence of deranged liver function within a few days of the start of VCR infusion. Because of the introduction of other potentially hepatotoxic agents, such as high-dose melphalan and total-body irradiation, shortly after VCR it was not possible to draw any conclusion about the relative contribution of VCR to subsequent liver dysfunction. Similarly, because of other treatment it was not possible to confirm a previous suggestion that VCR may cause dose-related myelosuppression.

In conclusion, it appears that a 5-day infusion of VCR is relatively well tolerated and allows dose escalation and prolongation of measurable VCR in the plasma. Because of the greater convenience of single bolus administration, comparative studies of effectiveness in relapsed patients or demonstration of activity in VCR-resistant disease is required before more widespread use of this approach can be considered.

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