

Original article

Nitroso-urea–cisplatin-based chemotherapy associated with valproate: Increase of haematologic toxicity

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Summary

Background: The incidence of haematologic toxicity of valproate (VPA) ranges from 1% to 32%, and consists mainly of asymptomatic, dose-dependent thrombopenia. We describe a potentiation of haematologic side-effects of nitroso-urea (NU) when prescribed in association with VPA.

Patients and methods: We followed a cohort of 70 patients (58 men, 22 women, mean age: 56 years, range 20–75 years). Patients with high-grade gliomas were treated with up-front chemotherapy regimen consisting of fotemustine (d3: 100 mg/m²), cisplatin (d1–3: 33 mg/m²) and etoposide (d1–3: 75 mg/m²) followed by whole brain radiotherapy at progression. Sixty patients required anti-epileptic drugs (AED) for either a single, well-documented epileptic seizure, or immediately initiated after neurosurgical procedures. AED included VPA (35 of 60), phenobarbital (PB) (17 of 60), carbamazepine

(CBZ) (2 of 60) and phenytoin (PHT) (3 of 60). Two patients had both PB and CBZ and one PB and PHT.

Results: Haematologic toxicity (grade 3–4 thrombopenia, neutropenia or both) was observed in 37 of 70 (52.85%) patients. Among them 24 (65%) had VPA. Group C were patients treated with fotemustine alone with or without VPA (23 patients).

Conclusion: When prescribed in association with a fotemustine-cisplatin regimen, VPA treatment results in a three-fold higher incidence of reversible thrombopenia, neutropenia or both. Haematologic side-effects decrease after AED modification during the continued chemotherapy. This adverse event should be managed with caution.

Key words: chemotherapy, haematologic toxicity, nitroso-urea, valproate

Introduction

Nitroso-urea (NU) and cisplatin (CDDP) are used in treatment of high-grade gliomas (HGG) and may have cumulated haematologic toxicity. Valproate (VPA) is a first-line antiepileptic drug (AED) frequently associated with other symptomatic medications in treatment of patients with brain tumours and seizures.

Thrombopenia is a well-known side-effect of AED and cytotoxic drugs. In order to document interactions, we analyzed retrospectively the haematologic side effects of different AED regimens, associated with the NU derivative fotemustine and CDDP.

Patients and methods

Seventy patients were treated for a HGG (52 glioblastomas, 11 anaplastic astrocytomas and 7 anaplastic oligodendrogliomas) after neurosurgical biopsy or partial resection (58 men, 22 women). Mean age was 56 years-old (range 20–75). Mean time of follow-up was 15 months.

An up-front chemotherapy regimen with fotemustine (day 3: 100 mg/m²), cisplatin (day 1–3: 33 mg/m²) and etoposide (day 1–3: 75 mg/m²) was administered to all patients. Haematological toxicity was systematically evaluated and classified from grade 1 to 4, as recommended by World Health Organisation (WHO) criteria. Conventional external brain radiotherapy (60 Gy) was prescribed after six cycles

of chemotherapy (day 1–28) or when haematologic toxicity or tumour progression appeared.

Sixty patients required AED, either for epileptic seizures (26 patients), or immediately after neurosurgery (31 patients). Ten patients had no AED.

Three groups of patients were studied:

- Group A consisted of patients treated with VPA: 35 patients, mean age 55.4 years. VPA was prescribed in monotherapy, with a mean dose of 1500 mg/d with plasma levels ranging from 40 to 100 mg/l.
- Group B consisted of patients without VPA treatment (others or no AED). 35 patients, mean age 56.5 years. Twenty-two patients in this group had monotherapy with either phenobarbital (PB, 17 patients), carbamazepine (CBZ, 2 patients), or phenytoin (PHT, 3 patients). Three patients had bitherapy, two with PB and CBZ and one with PHT and PB (Table 1).
- Group C consisted of patients treated without platinum salt but with NU in association or not with VPA: 23 patients (16 men, 7 women, mean age 53.2 years). Induction chemotherapy regimen consisted of fotemustine treatment (day 1, 8, 15: 100 mg/m²), followed by a month-cycle regimen: fotemustine (day 1–28, 100 mg/m²). Seventeen patients underwent VPA treatment.

Haematologic toxicity was evaluated systematically by weekly blood analysis during chemotherapy and afterwards, when thrombopenia and neutropenia were recorded. When grade 3–4 toxicity was observed, chemotherapy was postponed. Platelet transfusions were prescribed when platelet counts were below 10000/mm³ or in the case of bleeding and haemorrhaging (petechia, gingivoragia).

With comparison of groups A, B and C, we aim to compare consequences of VPA treatment in association with nitroso-urea associated or not with CDDP.

Table 1. Patient data.

F/CDDP/VP16 (n = 70)							F alone (n = 23)	
Group A	Group B						Group C	
VPA	No AED	PB	PHT	CBZ	PB+CBZ	PB+PHT	VPA	No AED
35	10	17	3	2	2	1	17	6

Table 2. Haematologic toxicity in group A (patients with VPA and F/CDDP/VP16).

Group A	Cycle 1	Cycle 2	Cycle 3	Total
Number of patients	35	31	23	89
Isolated neutropenia	2	1	0	3
Isolated thrombopenia	4 ^a	4 ^a	3	11
Neutropenia and thrombopenia	12 (34.3%) ^a	15 (43%) ^a	10 (43.5%) ^a	37
Platelet transfusions	5 (14.3%) ^a	8 (25.8%) ^a	6 (26%) ^a	19

^a $P < 0.001$.

Table 3. Haematologic toxicity in group B (F/CDDP/VP 16 without VPA).

Group B	Cycle 1	Cycle 2	Cycle 3	Total
Number of patients	35	33	27	95
Isolated neutropenia	2 (5.7%)	2 (6%)	2 (7.4%)	6
Isolated thrombopenia	0	0	2 (7.4%)	2
Neutropenia and thrombopenia	3 (8.57%)	3 (9%)	4 (14.8%)	10
Platelet transfusions	2	1	3	6

Table 4. Haematologic toxicity in group C.

FOTE and VPA / FOTE alone	Cycle 1	Cycle 2	Cycle 3	Total
Number of patients	17 / 5	16 / 5	15 / 5	48 / 15
Isolated neutropenia	1 / 0	1 / 0	1 / 0	3 / 0
Isolated thrombopenia	4 / 0	2 / 0	3 / 0	9 / 0
Neutropenia and thrombopenia	5 / 0	1 / 0	2 / 0	8 / 0
Platelet transfusion	4 / 0	2 / 0	0 / 0	6 / 0

Results

Mean toxicity was 55% in group A and 18.9% in group B. VPA appeared to increase the risk of haematologic toxicity by a factor of three ($P < 0.001$). The number of toxic events seems to be stable for the three first cycles (Table 2). For group B, toxicity seemed to be dose-dependent and increased after the third cycle, as usual for this chemotherapy regimen.

Tables 2 and 3 show the haematologic events in our patients during the first three-month cycles of chemotherapy (184 cycles; 68 cycles with haematologic toxicity). Isolated thrombopenia or neutropenia were rare. Rather,

both toxicities were usually observed. We noticed that in group A, neutropenia was more severe (grade 4) than in group B but patients recovered as quickly as in other cases with normal haematological rates. Thrombopenia was more acute and prolonged in group A (15 days *versus* 8 days). Consequently, the majority of patients in group A underwent fewer cycles of chemotherapy (m: 3) than in group B (m: 4).

The mean age of patients with haematologic toxicity was 56.8 years in group A and 64.5 years in group B. Age seems to be determinant for the haematologic toxicity of chemotherapy but not for potentiation of haematologic toxicity when chemotherapy is associated with VPA. According to our data in our study, patients recovered from haematologic side effects on the cycle that followed VPA withdrawal (or replacement with PHT or PB). Rechallenge with VPA was not performed. AED substitution allowed oncologists to continue cytotoxic treatment and respect dose-intensity.

In group C the haematological profile was dramatically different in patients with NU alone, where no toxicity was noted (Table 4). Haematologic toxicity occurred less frequently in the group with NU/VPA than in group A (NU/CDDP/VPA).

Discussion

Fotemustine is a diethyl-chloroethyl nitroso-urea used for treatment of metastatic melanoma and recurrent HGG. Its structure has been modified to increase liposolubility and cell intake. Usual posology is 100 mg/m²/q28d. Haematologic toxicity is frequently associated with NU treatment [2], including thrombopenia grade 3 (29%) or grade 4 (11%) and neutropenia grade 3 (46%) or 4 (14%). In the case of fotemustine, a similar adverse effect has been observed on blood cells [3]. Toxicity is delayed, transient and cumulative. Anaemia is unusual (grade 3: 11%). Cisplatin is a cis-diammine-dichloroplatine II often used in treatment of solid tumours. Haematologic toxicity of this drug is moderate. Etoposide is used in polychemotherapy in synergy with cisplatin. Leucopenia and thrombopenia are reported to range from 3% to 17%.

The incidence of haematologic toxicity of VPA ranges from 1% to 32% [4-6]. Toxicity consists mainly of asymptomatic, dose-dependent thrombopenia. This manifestation is never severe enough to discontinue therapy and patients respond to small decreases in dose

intensity [7]. Toxicity from VPA can be explained, at least in part, by a toxic effect on haematopoietic precursor or stem cells [8]. Leucopenia has been reported with VPA treatment whereas bone marrow aspirates and polynuclear antibodies are normal when explored [9].

In the present study, haematologic toxicity was more frequent (risk factor 2.9), severe and prolonged than the usual haematologic side-effects of nitroso-urea in patients with VPA-combined treatment (group A). This adverse event has already been described by Loiseau when VPA was associated with other AED (10) but interaction with chemotherapy (Fotemustine or other alkylating agents) has never been reported.

VPA-based treatment seems to increase haematologic toxicity of chemotherapy. It modified chemotherapy tolerance and regimen. More transfusions are prescribed with VPA-associated treatment. It can be easily reversed with alternate anti-epileptic drugs.

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