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Clinical Study

Fluctuation of serum phenytoin concentrations during autologous bone marrow transplant for primary central nervous system tumors

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Summary

We reviewed our experience for adult patients receiving oral anticonvulsant therapy during high-dose chemotherapy and autologous bone marrow re-infusion for primary malignant tumors of the central nervous system. Nineteen patients received either iv carmustine (BCNU) 900–1050 mg/m^2 and 6120 cGy cranial irradiation (N = 10), iv carmustine 900–1050 mg/m^2 and iv cisplatin 200 mg/m^2 (N = 8), or iv carmustine 600 mg/m^2, iv cisplatin 200 mg/m^2, and iv etoposide 2400 mg/m^2 (N = 1). Anticonvulsant therapy consisted of phenytoin alone (N = 8), phenobarbital alone (N = 4), carbamazepine alone (N = 2), phenytoin and carbamazepine (N = 2), carbamazepine and phenobarbital (N = 1), and no anticonvulsant therapy (N = 2). Serum anticonvulsant concentrations were monitored frequently and doses adjusted to keep values in the therapeutic range. While phenobarbital and carbamazepine doses remained relatively stable, all patients required increased doses of phenytoin anticonvulsant therapy after beginning chemotherapy (mean onset 3.7 days after initiation of chemotherapy). The increase in phenytoin dose ranged from 50% to 300% above baseline (mean 134%). By the time of discharge from the hospital (approximately 3–4 weeks after the start of chemotherapy) anticonvulsant dose was decreased to near pre-therapy levels. These swings coincided with the initiation of dexamethasone therapy for antiemetic effect and were more pronounced in patients also receiving cisplatin therapy. Due to close monitoring of serum phenytoin concentrations, no instances of toxicity due to excessive drug concentration, or seizures due to subtherapeutic doses, were noted in patients with primary CNS malignancies. Serum phenytoin concentrations fluctuate markedly during high-dose chemotherapy and must be analyzed frequently during the course of therapy.

Introduction

The treatment of malignant CNS (central nervous system) tumors remains sub-optimal. Median survival is less than one year and recurrent tumors have an even poorer prognosis [1–5]. In part, these observations relate to the fact that the 'blood-brain barrier' hampers effective delivery of drugs [6, 7] as well as the perception that these tumors are relatively insensitive to conventional doses of chemotherapy. One strategy to improve survival in patients with malignant CNS tumors is to re-infuse autologous bone marrow after the administration of high doses of chemotherapy in order to exploit the steep dose-response effect observed in experimental animal systems and possibly overcome the problem of penetrating the 'blood-brain' barrier [8, 9].

Most patients with primary or metastatic brain tumors require oral anticonvulsant therapy. We

noted in one metastatic malignant melanoma patient receiving phenytoin seizure prophylaxis that serum concentrations of this drug fluctuated markedly during autologous bone marrow transplantation. This patient's dose requirement more than doubled during the course of the transplant. After discharge, the patient developed symptoms strongly suggestive of recurrent CNS disease, which subsequently were shown to be due to phenytoin toxicity and markedly elevated serum concentrations. We, therefore, reviewed our experience for brain tumor patients receiving anticonvulsants during autologous marrow transplant.

Case report

A 45 year old white male developed clinical stage I, Clark's level III, truncal malignant melanoma in 1976. He had a recurrence in the right lung in 1983 for which he underwent a partial lobectomy. In 1985 he had partial resection of the left cerebral occipital lobe due to metastatic malignant melanoma. The patient was placed on phenytoin therapy for seizure prophylaxis after craniotomy. One month after initiating phenytoin treatment, he was admitted to University Hospitals of Cleveland in 1986 to undergo an autologous bone marrow transplant for a second lung recurrence. Carmustine (BCNU) 1050 mg/m^2 iv over 3 days and cisplatin 200 mg/m^2 iv over 5 days each in divided doses was used as the preparative regimen followed by autologous bone marrow re-infusion. During this hospital stay, the patient's phenytoin dose was increased from 400 mg per day to 900 mg per day to maintain serum phenytoin concentrations in the therapeutic range (total phenytoin 10–20 mg/L, free phenytoin 1.0–2.0 mg/L). The patient was discharged to home one month after transplant taking phenytoin 900 mg/day in divided dose. He was admitted to a community hospital one week after discharge because of nausea, vomiting, generalized weakness and diplopia. Recurrence of CNS malignant melanoma was strongly considered, but CT brain scan was unremarkable. A serum phenytoin concentration was found to be >30 mg/L. Phenytoin dose was withheld and then was re-started at 400 mg per day, and the patient's symptoms resolved.

Patients and methods

Nineteen patients, consisting of 18 consecutive patients from April 1987 through April 1990 with primary malignant CNS tumors and one malignant melanoma patient with resected brain metastases, underwent high-dose chemotherapy and autologous bone marrow transplantation at the Ireland Cancer Center of University Hospitals of Cleveland. Oral anticonvulsant therapy consisted of phenytoin alone (N = 8), phenobarbital alone (N = 4), carbamazepine (N = 2), phenytoin and carbamazepine (N = 2), carbamazepine and phenobarbital (N = 1), and no anticonvulsant therapy (N = 2). Patients were carefully monitored to assure that they were taking all oral anticonvulsant medications. Histologic diagnoses included: 5 cases of anaplastic astrocytoma, 12 cases of glioblastoma multiforme, one case of primary CNS lymphoma and one case of metastatic malignant melanoma with resected brain metastases. Eleven men and 8 women ages 19 to 59 years (median 31 years) were treated. The autologous bone marrow transplant protocols were approved by the Institutional Review Board for Human Investigation and the patients gave written informed consent for therapy.

In relapsed or refractory primary CNS tumors and in the malignant melanoma patient, the treatment regimen consisted of iv carmustine (300–350 mg/m^2/day for 3 consecutive days, e.g. days T-5 through T-3, or 5 days through 3 days before marrow re-infusion) plus iv cisplatin (40 mg/m^2/day for 5 consecutive days, e.g. days T-6 through T-2), followed by marrow re-infusion (day T-0) (N = 8) [10–11]. Patients with newly diagnosed tumors underwent therapy with iv carmustine 300–350 mg/m^2/day for 3 days, e.g. days T-5 through T-3, marrow autograft (day T-0), and one week later (day T+7) the initiation of involved-field cranial radiation given to a dose of 6120 cGy (N = 10) [12, 13]. The patient with central nervous system malignant lymphoma received iv cisplatin (40 mg/m^2/day for 5

consecutive days, e.g. days T-6 through T-2), iv carmustine (200 mg/m^2/day for 3 days, e.g. days T-5 through T-3) and iv etoposide (800 mg/m^2/day for 3 days, e.g. days T-5 through T-3) followed by autologous bone marrow reinfusion (day T-0) (N = 1) [14]. All but 5 patients were receiving dexamethasone therapy 4–40 mg per day) for cerebral edema prior to beginning chemotherapy, and most patients had the dose increased during hospitalization to prevent an increase in cerebral edema, presumably as a result of tumor injury (see Table 2). Eighteen patients received iv dexamethasone 10 mg one half-hour prior to and 6 hours after administration of chemotherapy for antiemetic effect [15]. The patients receiving cisplatin also received metoclopramide therapy 1–2 mg/kg iv every 2 hours; lorazepam, haloperidol, and prochlorperazine also were used as anti-emetics on an individual basis. Patients were cared for in single hospital rooms, had multi-lumen central venous catheters, were given frequent blood-component transfusions, and received antibacterial agents for treatment of neutropenic fever. Toxicities were graded according to the Common Toxicity Criteria of the National Cancer Institute.

Results

Seventeen of 19 patients, including the index patient with metastatic malignant melanoma cited in the case report UPN 228, i.e. unique patient number 228, received one or more oral anticonvulsants. Ten patients received phenytoin alone or in combination. In order to maintain serum phenytoin concentrations with the therapeutic range (total phenytoin 10–20 mg/L, free phenytoin 1.0–2.0 mg/L), the dose of phenytoin initially was increased in all ten patients including the patient described in the case report (Table 1). Free:total phenytoin serum concentration ratio remained constant in all patients. The percent increase of phenytoin dose above baseline (e.g. at the start of chemotherapy) varied from 50% to 300% (Table 1). This change in dosage was more pronounced in patients who received both cisplatin and carmustine (N = 5) (median 150% increase) compared with those receiving carmustine and radiation therapy (N = 5) (median 66% increase). One patient developed a generalized tonic-clonic seizure after the administration of high-dose chemotherapy. This development occurred probably due to an increase in cere-

Table 1. Modification of phenytoin daily dose in patients receiving phenytoin anticonvulsant therapy alone or incombination during autologous bone marrow transplant

Patient	UPN[a]	Dose prior to chemotherapy	Maximum dose	Percent change	Dose at discharge	Discharge dose percent reduction from maximum dose
1	851	400 mg	1000 mg	+ 150%	400 mg	60%
2	827	200 mg	800 mg	+ 300%	700 mg	12%
3	743	300 mg	600 mg	+ 100%	400 mg	33%
4*	671	400 mg	1000 mg	+ 150%	400 mg	60%
5	228	400 mg	900 mg	+ 125%	900 mg	0
6	680	300 mg	800 mg	+ 166%	350 mg	56%
7	727	300 mg	800 mg	+ 166%	450 mg	44%
8	677	400 mg	600 mg	+ 50%	300 mg	50%
9	867	300 mg	500 mg	+ 66%	300 mg	40%
10*	893	300 mg	460 mg	+ 55%	–	–
Median		300 mg	800 mg	125%	400 mg	44%
Range		200–400	460–1000 mg	50–300%	300–700 mg	12–60%[b]

* Pt received both phenytoin and carbamazepine. Patients 1–5 received carmustine 900–1050 mg/m^2 and cisplatin 200 mg/m^2 therapy, and patients 6–10 received carmustine 900–1050 mg/m^2 plus cranial irradiation. [a] Unique Patient Number assigned to each bone marrow transplant patient by the Ireland Cancer Center. [b] excludes patient UPN 228.

bral edema, documented on brain CT scan, presumably from tumor necrosis. The edema responded promptly to an increase in corticosteroid doses. At the time of the seizure, this patient had a serum phenytoin concentration in the therapeutic range, but had required a 100% increase in the dose of phenytoin a few days before in order to achieve that serum concentration. No seizures were observed in the other nine patients receiving phenytoin. All ten patients subsequently required a reduction in the phenytoin dose in order to maintain a level in the therapeutic range. There was no difference in the decrement of the phenytoin levels in the two populations (47% in cisplatin and carmustine group; 47% in carmustine alone group). There also was minimal change in the protein binding of phenytoin as exhibited by the free or unbound phenytoin concentration to total phenytoin concentration ratio.

Five patients received phenobarbitol therapy alone or in combination with carbamazepine. During the course of treatment, none of these patients required an increase in phenobarbitol dose to maintain the phenobarbital concentration in the therapeutic range. One patient (UPN 780) exhibited generalized grand mal seizures which responded to an increase in dexamethasone dosage without an adjustment in phenobarbital therapy. Two patients (UPN 676 and UPN 915) received carbamazepine alone for seizure prophylaxis. Neither of these patients had marked fluctuations (>20% change) in carbamazepine serum concentrations during hospitalization.

Two patients received carbamazepine therapy in addition to phenytoin, and both individuals required an increase in carbamazepine dosages (125% and 63%, respectively). One patient (UPN 893) was discharged to take carbamazepine alone at a dose that was 25% above the admission dose. The second patient (UPN 671) was discharged to receive carbamazepine at a dose 63% above the admission dose. Both patients also required increases in phenytoin dose of 55% and 150%, respectively.

Most patients had excellent control of chemotherapy-induced emesis. Of the 18 primary CNS malignancy patients treated, 11 patients had mild (grade I) nausea, vomiting, and diarrhea and the remaining 7 patients had no gastrointestinal toxicity. There was no correlation between gastrointestinal toxicity, phenytoin concentrations or individual chemotherapy regimens.

Patients treated with carmustine and cisplatin had received a median daily dose of 8 mg dexa-

Table 2. Dexamethasone doses prior to, during, and after completion of autologous marrow transplant, and at discharge in patients receiving phenytoin alone or in combination

Patient	UPN*	Daily dose prior to chemotherapy	During chemotherapy	Percent change dose/day	Duration of % change in dose (days)	Total dose during chemotherapy	Daily dose at discharge
1	851	4 mg	24 mg	500%	5	120 mg	0
2	827	16 mg	36 mg	125%	5	180 mg	32 mg
3	743	none	20 mg	–	5	100 mg	8 mg
4*	671	4 mg	24 mg	500%	5	120 mg	12 mg
5	680	40 mg	80 mg	100%	3	240 mg	2 mg
6	727	8 mg	28 mg	250%	3	84 mg	0
7	677	8 mg	28 mg	250%	3	84 mg	8 mg
8	867	8 mg	8 mg	0	0	8 mg	12 mg
9	228	none	20 mg	–	5	100 mg	8 mg
10*	893	8 mg	28 mg	250	5	84 mg	8 mg
Median		8	26	250%	5 days	100	8
Range		0–40	0–80	0–500	0–5 days	8–240	0–32

[a] Unique Patient Number assigned to each bone marrow transplant patient by the Ireland Cancer Center. * Received both phenytoin and carbamazepine.

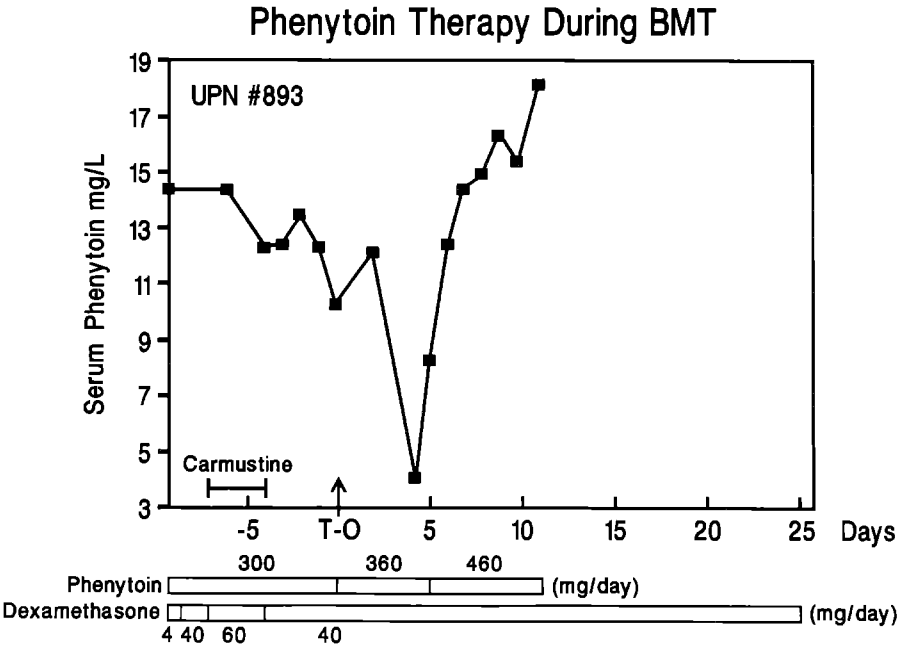

Fig. 1. Treatment course and fluctuation in serum phenytoin concentration for patient UPN 893. Note the marked increase in dexamethasone dose.

methasone prior to the administration of chemotherapy (Table 2). The median daily dosage of corticosteroid therapy during chemotherapy administration was 26 mg. This increased dose was administered a median of 5 days after the start of therapy. The dexamethasone dose increment above baseline varied from 0% to 500%. This change was more pronounced in patients who received the cisplatin and carmustine combination (median 500%) compared to the carmustine alone group (median 250%). This difference may be attributed to the additional dexamethasone given as an antiemetic in the combination 5 day therapy as opposed to the single drug 3 day regimen.

Figure 1 shows a representative treatment course and fluctuation in serum phenytoin concentration in one patient during autologous bone marrow transplant (UPN 893). This patient received both phenytoin and carbamazepine therapy during high-dose carmustine and autologous bone marrow reinfusion. The phenytoin dose was increased more than 50%, and the serum concentration of this agent varied widely. The marked increase in dexamethasone dose (from 4 to 60 mg per day) also is shown. Phenytoin therapy was discontinued at the request of the patient's neurosurgeon at the time of discharge.

Comments

Phenytoin is 80–90% absorbed after oral administration and is widely distributed via plasma protein binding [16, 17]. Metabolism is predominantly by hepatic microsomal enzymes and less than 4% of the administered dose is excreted unchanged in the urine. Phenytoin serum concentrations, however, are influenced by changes in absorption, metabolism, protein binding or the use of many agents such as cancer chemotherapeutic agents and antibiotics [18–21].

We noted that as early as 3 days (mean 3.7 days) after the administration of the high-dose carmustine-containing regimens, phenytoin serum concentrations decreased to subtherapeutic levels. Therefore it was necessary to increase the dose of the phenytoin over the 2 weeks after the administration of chemotherapy. Another important ob-

servation is the need then to reduce the elevated phenytoin dose after an approximately 2–3 week period to prevent clinical toxicities due to the subsequent rise in phenytoin serum concentrations at that time.

We believe these findings may result from at least two different mechanisms: (1) an effect of cisplatin on the absorption of phenytoin from the gastrointestinal tract and (2) the acceleration of the metabolism of phenytoin due to dexamethasone. This speculation is further supported by the fact that phenytoin dosage requirement was higher in patients who received cisplatin along with carmustine than in those receiving carmustine alone (150% in carmustine-cisplatin group vs 66% in carmustine only group). Besides the addition of cisplatin, these patients also received higher doses of dexamethasone (median 500% in carmustine-cisplatin group vs 250% in carmustine only group). This increase likely is secondary to the use of dexamethasone as an antiemetic agent given for the 5 days of the carmustine plus cisplatin treatment regimen vs. 3 days of treatment with the carmustine alone regimen.

The increased metabolism of phenytoin due to glucocorticoid therapy and the need to increase dosage has been reported [22]. Wong and co-workers [22] retrospectively reviewed phenytoin dose in 40 brain tumor patients. They analyzed many variables including age, diagnosis, smoking history, liver function tests, phenytoin-dexamethasone dosage, and administration of other drugs and related these characteristics to changes in phenytoin concentrations. None of the parameters examined approached statistical significance except for the concurrent use of phenytoin and dexamethasone. In 6 patients who were receiving a constant phenytoin dose, the addition of dexamethasone therapy resulted in statistically significant lowering of the serum phenytoin concentration. In addition, 5 case reports have been published describing altered phenytoin pharmacokinetics after a variety of cisplatin-containing chemotherapy regimens [23–27]. In 3 of these reports [23–25], the authors believed that the decline in serum phenytoin concentrations resulted from reduced absorption of oral phenytoin as a consequence of the chemotherapy. All three reports described chemotherapy regimens which included cisplatin. On the other hand, in two other studies pharmacokinetic analysis suggested an increase in the metabolism of phenytoin as the cause for these findings [26, 27]. These two latter reports showed an increase in phenytoin requirements even though the patients were changed to intravenous phenytoin.

A recent publication addressed decreased phenytoin serum concentrations in patients with CNS tumors who received conventional doses of carmustine (40 mg/m^2/day for 3 days) and cisplatin (40 mg/m^2/day for 3 days) [28]. In those patients who received at least three cycles of continuous-infusion carmustine and cisplatin, an increase in the daily phenytoin dose was required to maintain therapeutic levels. The magnitude of this dosage increase averaged 41%. In a corresponding group of patients who received carmustine only, the authors did not observe a significant change in the serum phenytoin levels. In that study, phenobarbital serum concentrations did not change significantly in any patient [28].

We believe the most likely explanation for our findings is an increase in the metabolism of phenytoin along with a possible decrease in gastrointestinal absorption. A change in protein binding can be excluded as causal since the free:total phenytoin serum concentration ratio was constant in all patients. A selective decrease in drug absorption has been previously described and is substantiated in light of the fact that phenobarbital concentrations remaining stable in all 5 patients who received this drug by the oral route [25]. Also, in 3 of 5 patients who received oral carbamazepine therapy, dose increase was not necessary.

With the development of newer chemotherapeutic regimens for malignant CNS lesions, the interaction of anticonvulsants, chemotherapy and corticosteroids is of increasing importance. Subtherapeutic or toxic serum levels of phenytoin can be avoided by anticipating changes in the neuroleptic drug levels and modifying dosage requirements accordingly in the course of treatment. Phenytoin serum concentrations should be monitored at regular intervals (e.g. every 2 to 3 days during and after the administration of chemotherapy and corticos-

teroid therapy). Further studies are necessary to define the mechanism(s) that account for the fluctuations in phenytoin levels and to identify the chemotherapeutic agents that may predispose patients to these alterations in phenytoin pharmacology.

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