Increased Vulnerability of the Spinal Cord to Radiation or Intrathecal Chemotherapy During Adolescence: A Report From the Children's Oncology Group

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Purpose. To assess the rate of spinal cord toxicity in adolescents resulting from chemoradiotherapy of parameningeal sarcoma. ***Methods and Materials.*** Of 152 patients with parameningeal sarcoma treated per the Intergroup Rhabdomyosarcoma Study Group protocol from 1977 through 1989, eight developed paralyzing ascending myelitis after intrathecal chemotherapy with cytosine arabinoside, methotrexate, and hydrocortisone administered during and after radiation therapy to volumes that included part of the spinal cord. The eight cases include three not previously published. ***Results.*** Of eight patients who developed CNS toxicity after intrathecal chemotherapy and radiotherapy for parameningeal rhabdomyosarcoma, all but one were between 13 and 18 years of age when treated. This severe toxicity occurred in one quarter of 28 adolescents treated with the regimen in comparison with one of 123 children 12 years of age or less ($P < 0.0001$), a rate that was as much as 30 times higher in the adolescents. Lengthening of the spinal cord during the pubertal growth spurt may account for the apparent increased vulnerability. ***Conclusions.*** Chemoradiotoxicity-associated spinal cord injury appears to be more likely to occur in adolescents than in younger or older ages. This observation appears to reverse a conventional wisdom in which the central nervous system is thought to become more resistant to the neurotoxic effects of chemoradiotherapy as it matures. Pediatr Blood Cancer

Key words: adolescence; intrathecal chemotherapy; radiation myelopathy; sarcoma; spinal cord

INTRODUCTION

Since the first report of radiation myelitis by Ahlbom [1] over 60 years ago, it is well-known that the spinal cord is highly sensitive to ionizing radiation. There are several reports in the literature on recommended radiation dose limits for the spinal cord, primarily for the adult population [2–4]. It is generally accepted that the cord tolerance is dependent upon multiple factors, including length of cord irradiated, fraction size, and the addition of systemic or intrathecal chemotherapy. However, the relationship of cord tolerance to patient age has not been well established. It has been commonly assumed that the spinal cord is most sensitive to cancer therapy at the youngest ages and becomes more tolerant as the patient grows into adolescence and adulthood but this phenomenon has not been formally studied.

Chemotherapy and RT are particularly important in treating parameningeal sarcomas, as extensive surgical intervention is precluded by proximity to vital structures and cosmetic concerns. Typically, in the absence of intracranial extension or brain metastases, two to three cycles of chemotherapy are administered prior to RT. RT to the tumor volume plus an adequate margin of 2–5 cm of normal tissue is then administered over 4–6 weeks in daily fractions of 1.8–2 Gy for a minimum total dose of 50 Gy [5–9]. Patients with meningeal extension of rhabdomyosarcoma (RMS) require more rigorous chemotherapy and RT regimens to achieve good disease control. To address this problem, the Intergroup Rhabdomyosarcoma Study Group (IRSG) developed a program in 1977 to administer intensive intrathecal chemotherapy (ITC) in combination with systemic chemotherapy and RT to portions of the CNS for patients younger than 21 years of age who had cranial parameningeal sarcoma with meningeal extension [10].

In 1992, the group reported that five of 149 patients treated under the protocol sustained permanent spinal cord damage as a sequela of therapy [11]. The report made no mention of the fact that four of the five patients were adolescents, ranging in age from 14 to 17 years. Since then, we have identified three additional patients who suffered spinal cord damage after the administration of similar multimodality therapy for parameningeal sarcoma, all of whom were within the same age range. In this report, we summarize the findings from all patients exhibiting chemoradiation-induced spinal cord symptoms.

MATERIALS AND METHODS

We reviewed the records of 152 patients treated on or according to IRSG regimens from 1977 to 1989 that indicated ITC for prevention or treatment of meningeal extension of sarcoma located in parameningeal sites. Eligibility requirements for this retrospective study included: age less than 21 years, diagnosis of cranial parameningeal sarcoma with signs of meningeal impingement (cranial nerve palsy, bony erosion at the cranial base, intracranial spread in contiguity with the primary tumor, tumor cells in the

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cerebrospinal fluid (CSF), and/or spinal cord block), and no previous therapy. We extracted data for all patients with evidence of ascending myelitis subsequent to ITC and cranial and/or spinal RT. Five of these patients were previously described in detail by Raney et al. [11]. Since then, three more patients with paraspinal sarcoma who developed ascending myelopathies under similar circumstances have been identified. Chi-square and Fisher exact tests were used for rate comparisons.

RESULTS

Demographic characteristics of the eight patients who developed myelitis are summarized in Table I. All eight received intrathecal AraC, MTX, and HC during and after RT to the base of the brain, spinal cord, or both. The individual doses of AraC were 60 mg/m^2 in seven patients, while a single patient received 50 mg/m^2 without an upper limit. In seven patients, the dose of MTX was 15 mg/m^2 with an upper limit of 15 mg, and in one (#8) it was 12 mg/m^2. The dose of HC is shown in Table I. All but one of the patients (#8) received leucovorin the day after IT MTX. RT was to the base of the brain in five, whole brain in four, whole spine in two, craniocervical in one, and partial spine in three. The RT doses are specified in Table I.

Five of these patients (#1–5 in Table I) were previously described in detail by Raney et al. [11]. None had evidence of lower extremity or sphincter impairment at diagnosis. Within 5–9 months of the start of therapy, these patients developed loss of sphincter control and inability to walk; this progressed to severe flaccid quadriparesis and necessitated long-term ventilatory support in four. All five received systemic vincristine (VCR), actinomycin-D (ActD), cyclophosphamide (CY), and doxorubicin (DOX); four received cisplatin (CDDP); and three received etoposide (VP16). All five received 47–55 Gy to the primary tumor at the base of the brain; four received 30 Gy of cranial RT; three received cervical lymph node RT; and three received spinal RT. All five received four to seven courses of triple ITC with cytosine arabinoside (AraC), methotrexate (MTX), and hydrocortisone (HC). Three patients died, including one after local tumor recurrence with CNS extension and two without known recurrence. In one of the latter patients, the results of an autopsy showed necrosis of the cervical spinal cord and caudal medulla.

Since the publication of the report of these five patients [11], we have identified three additional patients (#6–8 in Table I) who developed ascending myelitis after ITC and RT. All three had paraspinal primaries, presented with symptoms of spinal cord impingement, and received spinal RT and the same triple ITC regimen of AraC, MTX, and HC. Two (#6 and #7 in Table I) of the three were mentioned in an amendment to the IRS-III trial on June 5, 1987 that reduced the number and dosages of ITC but were not included in prior reports [11,12] since these patient's prior spinal cord compromise may have confounded interpretation of myelitis pathogenesis in the original reported group of patients without spinal cord compression. With initial surgery and RT, the spinal cord symptoms in these two patients had resolved before the onset of treatment-related myelopathy.

The third patient (#8 in Table I) was treated during the same era but protected from review until recently by a medical-legal injunction. She was not entered into an IRSG trial but treated according to the IRS-III trial [11] with 46 Gy to the upper spinal cord, a course of intravenous ActD, and triple ITC with AraC, MTX, and HC during and after RT. She became paraplegic, paretic in both upper extremities, and incontinent of bowel and bladder function.

Seven of the eight patients who developed ascending myelitis were adolescents between 13 and 18 years old, and one patient was 6 years old, when treated with ITC and RT that included the spinal cord. Of the total number of patients with high risk parameningeal primaries treated by the IRSG regimen, 124 were less than 13 years of age, and 28 were over 13 years of age. Thus, 25% of adolescent patients aged 13–21 years developed chemoradiation myelitis, in contrast to $<1\%$ of those who were younger than 13, implying that the relative rate of myelitis in the adolescent patients was in the range of 30-fold higher than in younger patients ($P < 0.0001$ by both Fisher exact test and χ^2 [=22.18 with Yates correction]).

DISCUSSION

Paralyzing ascending myelitis associated with treatment of tumors located within or in proximity to the CNS can result from chemotherapy, RT, or both [13]. Ahlbom first reported radiation myelitis over 60 years ago [1]. Since that time, various recommendations on radiation tolerance limits of the human spinal cord have been published, generally as a dose-dependent phenomenon [2–4]. Several reports also stress the impact of number of fractions, fraction size, overall time, and volume irradiated on the incidence of myelitis after spinal cord irradiation [14–19]. The most widely observed dose limit for the adult spinal cord is 45 Gy in 22–25 fractions [4,20,21]. It is estimated that the 45 Gy regimen yields an incidence of myelopathy of $\leq 0.2\%$ while doses between 57–61 and 68–73 Gy yield incidences of 5% and 50%, respectively [22–24]. Factors lowering spinal cord tolerance to radiation include prior spinal cord pathology, combination chemotherapy, and immunocompromised status [3].

ITC also has been associated with varying degrees of neurotoxicity [25–30]. Myelitis has been detected after systemic administration of high-dose AraC and concomitant IT cytosine in two of five children treated for Burkitt's lymphoma [31]. Another report described the case of a 14-year-old boy with acute lymphoblastic leukemia (ALL) who developed acute ascending myelitis followed by encephalopathy after receiving a second boost of IT MTX and AraC in standard doses (15 and 50 mg, respectively) [32]. It was unclear whether concurrent systemic chemotherapy with intravenous AraC might have worsened this boy's clinical condition.

ITC-associated spinal cord toxicity also develops in the absence of concurrent systemic chemotherapy or RT. Crawford et al. [33] described a 20-year-old male who developed ascending myelopathy with seizures within 48 hr of receiving 80 mg IT AraC. Resar et al. [28] published a second case report describing a 16-year-old boy with B-cell leukemia who developed acute encephalomyelopathy 20 hr after the third dose of AraC administered consecutively for 3 days. In both cases, the patients did not receive concurrent systemic chemotherapy or RT; it is, however, possible that high dosage and frequent administration of ITC were causative factors.

Simultaneous administration of RT and chemotherapy may reduce spinal cord radiation tolerance, but the combined effects for sequential therapy are impossible to predict because of confounding factors, such as timing, drug dose, and uptake. Concerns about combining neurotoxic ITC with RT have been emphasized in the literature [34–36]. AraC was shown to decrease the ED_{50} in rats when given intrathecally [37]. In humans, the association of MTX

TABLE I. Characteristics and Clinical Course of Patients With Severe Ascending/Transverse Myelitis

Pt[a]	Age (years)	Gender	Primary site and CNS extension[b]	Clinical group (stage)	Pathologic type[c]	IRSG regimen	Radiothherapy (Gy)				IT therapy mg/m^2 × no. of doses			Systemic chemotherapy[d]	Myelopathy latency[e] (months)
							Primary	Brain	Spine	Other	MTX[f]	Ara-C[f]	HC[f]		
1	17	F	NP, CNP, CBBE	III	Alv	II-26	52.6	30.6	30.0	Cerv LNs[j] 30.0	15 × 3	60 × 3	30 × 3	VCR; ActD; CPM	5
2	17	M	SS, CNP, CBBE, ICE	III	Emb	III-35	55.0	29.0	[i]	[i]	15 × 3	60 × 3	30 × 3	VCR; ActD; CPM; Dox; CPT;VP16	7
3	15	M	NP, CBBE, ICE	III	Emb	III-36	47.7	30.0	[i]	Cerv LNs[j] 50.4	15 × 3	60 × 3	30 × 3	VCR; ActD; CPM; Dox; CPT;VP16; DTIC	7
4	6	M	MEM, CNP, CBBE	III	Emb	III-36	50.4	[i]	[i]	Cerv LNs[j] 46.9	15 × 4	60 × 4	30 × 4	VCR; ActD; CPM; Dox; CPT;VP16; DTIC	8
5	14	F	NP. CBBE, CSF, Lungs	III	RMS	III-36	50.0	30.0	30.0	Lung 18.5	15 × 4	60 × 4	30 × 4	VCR; ActD; CPM; Dox; CPT;VP16; DTIC	7
6	13	F[g]	Paraspinal	III	RMS	II-26	50.4[h]	[i]	[i]	[i]	15 × 3	60 × 3	30 × 3	VCR; ActD; CPM	[g]
7	16	M[g]	Paraspinal	III	RMS	II-26	50.4[h]	[i]	[i]	[i]	15 × 3	60 × 3	30 × 3	VCR; ActD; CPM	[g]
8	13	F	C7 Brachial Plexus	III	EOE	II-26	[i]	[i]	46.2	[i]	12 × 5	50 × 4	50 × 5	VCR, ActD, CPM	4

[a]Patient number; [b]NP, nasopharynx; SS, sphenoid sinus; CNP, cranial nerve palsy; CBBE, cranial base bone erosion; ICE, intracranial extension; MEM, mastoid/middle ear; CSF, cerebrospinal fluid; [c]Alv, alveolar rhabdomyosarcoma; Emb, embyonal rhabdomyosarcoma; RMS, rhabdomyosarcoma, histology not specified; EOE, extra osseous Ewing sarcoma/primitive neuroectodermal tumor; [d]VCR, vincristine; ActD, actinomycin: D; Dox, doxorubicin (Adriamycin); CPM, cyclophosphamide; CPT, cisplatin; VP16, etoposide; [e]Time from therapy initiation to onset of symptoms; [f]MTX, methotrexate (top dose 15 mg); AraC, cytosine arabinoside, HC, hydrocortisone; [g]Values uncertain from available records; [h]Non-confirmed, protocol-prescribed dose (paraspinal); [i]RT dose = 0, except for potential scatter from adjacent targeted fields; [j]Cervical lymph nodes.

and irradiation in producing diffuse white matter necrosis is particularly known in the pediatric ALL population where prior irradiation allows MTX to enter the brain by altering the blood brain barrier. Safe doses of irradiation or MTX become toxic when combined with IT and systemic routes [36,38–42].

In 1977, the IRSG initiated a program of early, wide-field RT to the CNS and repeated lumbar IT medications along with systemic chemotherapy for patients younger than 21 years of age with cranial parameningeal sarcoma and a high risk of meningeal extension. From 1977 until 1987, 152 eligible patients with high-risk cranial parameningeal sarcoma were enrolled in IRSG trials. No additional cases have been reported to the IRS since the protocol was revised in 1987 to reduce the doses of the IT drugs and to limit them to four courses each. Nor has it been reported since the ITC was discontinued altogether by the IRSG in 1991, except for the rare patient with evidence for malignant cells in the cerebrospinal fluid [43]. The use of RT to brain and spinal cord has continued since then as previously prescribed without further reports of clinically significant myelitis in the IRSG trials or those continued by the Children's Oncology Group when the IRSG was subsumed by the latter organization. These observations lend support to the hypothesis that ITC was a major contributing factor to the myelopathy in the cases described in this report.

On the other hand, the RT could be the inciting agent in the patients reported here with ITC either decreasing cord tolerance to RT (synergistic toxicity) or adding sufficient toxicity of its own to render the myelopathy clinical significant (additive toxicity). Also, that three of the eight patients reported here presented with signs of spinal cord compression at the time of their original diagnosis of sarcoma, previous spinal cord compromise may also be a potential confounding factor. That the original symptoms and signs of cord compression abated before the subsequent onset of myelitis does not eliminate this factor in the three patients so affected.

When the original report of ITC-RT ascending myelopathy was reported in 1992 [11], an age relationship was not noted. It was the addition of the three patients in the current study that led to the observation, for the first time, that patient age appears to be a factor in the pathogenesis of ascending myelopathy, increasing the risk by as much as 25-fold or more in adolescents in comparison with younger patients. Only one of the eight patients was not a teenager between 13 and 18 years of age. The one patient with myelopathy who was less than 12 years of age was treated on the same regimen as several of the adolescent patients, albeit the actual volume of RT was smaller since he was smaller (6-year-old child vs. adolescent). That he received intravenously four known radiosensitizers (actinomycin-D, doxorubicin, cisplatin and DTIC [an analogue of temozolamide, an established radiosensitizer]) and one that is also probably a radiosensitizer (etoposide) may explain why this young patient also sustained a myelopathy, since only two of the other (older) patients received as many radiosensitizers. Also, he and only one of the adolescent patients received the largest number of doses of intrathecal chemotherapy. Alternatively, he may have had a DNA repair deficit or another RT/chemotherapy-sensitizing polymorphism that was not clinically recognized. The small number of patients and the variability in the location of the primary tumor and in the volume of RT, ranging from short (proximity of base of skull) to long segments of the spinal cord, prevented further analysis of the relationship of tumor topography and level/volume of cord irradiation.

We anticipated that younger children would develop CNS dysfunction at a greater rate than older children given the traditional views that the spinal cord is more vulnerable at younger ages [44–48]. On the basis of the analysis, though, we found that adolescents had a statistically significantly higher rate of spinal cord toxicity than their counterparts of 12 years old or younger, and that their rate was approximately 30 times higher under the circumstances described. This finding suggests that RT and/or ITC dose reduction in adolescents should be made as they are at substantially higher risk for spinal cord toxicity. Given that all of the patients in our experience had RT that included the spinal cord and all had clinical signs of myelitis emanating from the irradiated segment of the cord, we prefer to recommend that the preference for the dose reduction be applied to the RT.

That the mechanism of radiation-induced myelopathy is age-dependent has been observed in a well characterized rat model established by van der Kogel [19] at the University of Nijmegen Institute of Radiotherapy. Using a single fraction to the cervical cord, they found that the ED50 for white matter necrosis was significantly lower (19.5 Gy; 95% CI 18.7, 20.3 Gy) in infant rats <1 week of age than it was in juvenile and adult rats ≥ 2 weeks of age (mean 21.4 Gy; 95% CI 21.0, 21.7 Gy) [49]. The latency to the development of paresis increased steadily as function of age at irradiation, from about 2 weeks in 1-week-old, weanling animals to 6–8 months in adult animals ≥ 8 weeks of age. Whereas white matter damage was similar at all ages, expression of vascular damage depended on the age at irradiation. No vascular damage was observed in 1-week-old rats. Altered blood vessels were seen in juvenile animals irradiated at 3 weeks of age, and vascular necrosis occurred in adults rats irradiated at ≥ 8 weeks of age. The investigators concluded that the vasculopathy and latency are clearly age dependent, and that white matter damage and vascular damage are separate phenomena contributing to the development of radiation myelopathy, expression of which depends on the radiation dose applied and the age at irradiation [49]. We expect that the interaction of chemotherapy with these radiation-induced mechanisms of neurotoxicity is also age-related.

One explanation for the ascending nature of the myelopathy, when it is a primary clinical manifestation, is that the longest axons are the most vulnerable and thereby those to and form the lower extremities and bladder and bowel are affected first. Another is that intralumbar chemotherapy results in a concentration gradient from the lumbar to cervical levels and thereby the distal spinal cord has the earliest manifestations. When a myelopathy develops after irradiation of a relatively short segment of the cord, as occurred in patients #3, #4, and #8 in our series, the former explanation seems more likely than the latter.

Furthermore, we hypothesize that the increased rate of neurotoxicity during adolescence is due to increased vulnerability of the spinal cord as it lengthens during the adolescent growth spurt. During the adolescent growth spurt, the spinal cord lengthens by as much as 15 cm in males and 10 cm in females [50,51]. Females undergo this acceleration a year or two earlier than males, between 12 and 16 years and between 13 and 18 years in females and males, respectively. Proliferation of myelin sheath cells is required as the neurons elongate and may thereby render the cord susceptible to white matter necrosis, a hallmark of the myelopathy from RT and cancer chemotherapy agents.

If true, this paradigm challenges the common belief that the CNS becomes less vulnerable to cancer therapy (RT and chemotherapy)

as it matures during childhood and adolescence. From the findings in this report, we propose that the spinal cord is more susceptible to the cytotoxicities of cancer therapies during adolescence than at either earlier or later ages. Our study points to the need for more studies focusing on spinal cord tolerance in adolescents as a distinct population from adult or child cancer patients. Our observations should raise concern about the application of published spinal cord tolerance limits to the adolescent patient, especially when used in conjunction with radiosensitizing and radiorecall agents such as AraC, MTX, ActD, anthracyclines and platinating drugs.

Adolescents with primary CNS tumors that require spinal radiotherapy and chemotherapy have not been reported to have the rate of myelopathy observed in the sarcoma patients reported here. One explanation is that the CNS tumor patients have not been treated, in comparison to the sarcoma patients reported here, as aggressively with RT, triple ITC and multiple systemically administered recall or radiosensitizing agents like ActD, anthracyclines, MTX, araC, platinating agents and etoposide. If primary CNS tumor patient requiring high-dose spinal irradiation had been treated as aggressively, the incidence of ascending myelopathy might have been noted in them as well. One lesson of this report is that aggressive therapy with combined RT and triple ITC should be used more cautiously in the adolescent patient, which in the current era of increasing use of combined modality therapy and potential use of both systemic and intrathecal radiosensitizers in patients with metastatic primary CNS neoplasms, may have increased relevance.

In light of these findings, we recommend consideration of a lower spinal RT total dose or dose rate for adolescent patients who will also be receiving these known radiosensitizing chemotherapeutic agents, or as in the IRSG experience, continued limitation of direct cord exposure to IT MTX and IT AraC, especially when the spinal cord is also exposed to RT.

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