Cisplatin-Based Chemotherapy Followed By Focal, Reduced-Dose Irradiation For Pediatric Primary Central Nervous System Germinomas

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Summary: The objective of this study was to evaluate retrospectively one institution's experience treating pediatric central nervous system (CNS) pure germinomas with platinum-based chemotherapy followed by focal, reduced-dose irradiation. Eight patients were identified with localized, pure CNS germinomas from 1993 to 2004 at the authors' institution. The median age at diagnosis was 13 years (range 7–19). The median follow-up was 40 months (range 8–141). The tumor location was suprasellar in four, the pineal region in three, and the third ventricle in one. Irradiation was started a median of 20 weeks (range 17–22) from diagnosis and consisted of conformal fields to the primary site as determined by the initial diagnostic MR plus a 1.5- to 2-cm margin. Six of the eight patients received a dose of 3,060 cGy; two patients received 3,600 cGy. The 5-year actuarial event free survival was 71% (56–86%, 95% CI). Two patients suffered marginal (at field edge) failures and both were salvaged using reinduction platinum-based chemotherapy followed by cranial spinal irradiation and a boost to the primary tumor. The 5-year actuarial overall survival was 100%. There were no spinal failures. These data suggest that a reduction in both volume and dose (30.6–36 Gy) retains the excellent survival rates for patients with localized, pure germinomas of the CNS. A higher rate of ventricular relapse rate is observed, although salvage of those patients is feasible.

Key Words: central nervous system germinoma, radiotherapy, chemotherapy, pediatric germinoma

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Pure intracranial germinomas are a rare malignancy in childhood, accounting for only 1% to 2% of all primary central nervous system tumors (CNS). The standard treatment for years has been radiotherapy after histologic confirmation of the CNS mass.[1–8] Outcomes from this approach have been excellent, with survival rates of 90% to 100%.[1,3,4,6,8,9] Several relatively recent reports have suggested that the dose used and volumes treated may be reduced without compromising the event-free survival rate. Although controversy exists regarding the extent of radiotherapy (craniospinal irradiation [CSI] vs. whole ventricular vs. focal), there is evidence to suggest that CSI may be necessary only for patients having evidence of spread to the cerebrospinal fluid (CSF).

The long-term consequences of CSI or whole-brain irradiation in children with CNS pure germinomas have been examined by several authors. Merchant et al[6] reported substantial hormonal deficits prior to any treatment and after treatment with CSI but no long-term decrease in neurocognitive functioning or stature. Sawamura et al[10] reported CT or MR changes in 19 of 111 patients treated with large-volume irradiation for germ cell tumors (all histologies), and 7 of those patients showed various degrees of neurocognitive dysfunction. In addition, the estimated incidence of secondary malignancies was 16.8% at 19 years.

Attempts to forgo the potential complications of irradiation have led to attempts to treat with chemotherapy alone. The relapse rate, however, was high (48% at 5 years, crude rate) with this approach,[11] and the authors cautioned against the use of chemotherapy-only protocols outside clinical studies; this has been confirmed in more recent reports.[12] The use of combined modality therapy consisting of chemotherapy followed by radiotherapy recently has been examined, with promising results.[13–19] Although different doses and schedules have been used, all studies have used cisplatin (CDDP)-based regimens. High complete response (CR) rates have been achieved after three or four cycles of chemotherapy, and a reduced-dose and -volume approach for radiotherapy has been used in these trials.

We report our institutional experience treating patients with localized, pure germinomas with combination chemotherapy followed by reduced-dose and -volume radiotherapy.

METHODS

The charts of all patients treated for intracranial pure germinomas at our institution from 1993 to 2004 were reviewed. Eight consecutive patients were identified who were treated for localized, pure CNS germinomas. During this period two additional patients were diagnosed with multifocal germinoma and treated with CSI. Selected patient characteristics are shown in Table 1. The median age at diagnosis was

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TABLE 1. Patient Characteristics

Pt. No.	Age	Site of Disease	Extent of Surgical Resection	CTX Regimen	Dose (Gy)	Site of Failure	Shunt	CSF Markers	Serum Markers
1	13	Suprasellar	Biopsy	CaE × 4	30.6	None	VC	Negative	Negative
2*	7	Pineal	Subtotal	CaE × 4	30.6	A/PBE	VC	Not done	Negative
3	13	Pineal	Biopsy	CiEB × 3	30.6	None	VP	Negative	Negative
4	14	Suprasellar	Biopsy	CiEB × 2†	30.6	ABE	None	Negative	Negative
5	13	Suprasellar	Subtotal	CaE × 4	36	None	None	Not done	Negative
6	11	Third ventricle	Biopsy	CaE × 4	30.6	None	VP	Negative	Negative
7	13	Suprasellar	Gross total	CaE × 4	36	None	None	Negative	Negative
8	13	Pineal	Biopsy	CaE × 4	30.6	None	VC	Negative	Negative

*Patient 2 had DI and a pineal mass, no sellar or suprasellar mass.
†Patient declined further cycles due to toxicity.
Ca, carboplatin; Ci, cisplatin; E, etoposide; B, bleomycin; A/PBE, anterior and posterior block edge along ventricle (the anterior failure was well away from the sella); ABE, anterior block edge; VC, ventricular catheter, external; VP, ventriculoperitoneal.

12 years (range 7–19). The male to female ratio was 1:1. The median follow-up from diagnosis was 57 months (range 8–139). There were four suprasellar tumors and three in the pineal region, and one arose from the floor of the third ventricle. All patients had staging spinal MRIs as well as CSF sampling, which were negative for disease. Serum markers for alpha fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG) were negative in all patients. CSF markers (β-HCG and AFP) were obtained for six of the eight patients and were negative in all six. Histologic diagnosis was obtained in all eight patients: five had endoscopic or stereotactic biopsies and three had surgical resections (<90% tumor resection). The four patients with tumors in the suprasellar region had panhypopituitarism, including diabetes insipidus (DI) at diagnosis. One patient with a pineal region tumor presented with DI and no evidence of tumor in the suprasellar region. The remaining three patients had no pituitary dysfunction at diagnosis.

Chemotherapy

Patients were treated with two to four cycles of a platinum-based chemotherapy regimen. Five patients received four cycles of carboplatin (500 mg/m^2 for 2 days) and etoposide (100 mg/m^2 for 3 days); two patients received three cycles of CDDP (20 mg/m^2 for 5 days), etoposide (100 mg/m^2 for 5 days), and bleomycin (15 units/m^2 for 1 day); one patient received two cycles of a planned three-cycle regimen of carboplatin, etoposide, and bleomycin. This patient's parents elected to forgo the final cycle of chemotherapy because of toxicity considerations.

Evaluation of Response to Chemotherapy

Response to chemotherapy was documented after the third or fourth cycle of treatment. Five patients had a CR to chemotherapy as assessed by MR imaging on the completion of chemotherapy. Two patients with pineal region tumors had remaining "streak artifacts" that were considered to represent CRs. The remaining patient with a pineal region tumor had a residual abnormality of less than 1 cm on MR, which was nonenhancing and negative by PET scan; this patient was considered to have a "near-total response."

Radiotherapy

Volume

The target volume (defined as the GTV after 2000 according to the International Commission on Radiation Units and Measurements guidelines) was defined as the pre-chemotherapy T1 + gadolinium enhancing region. A 1.5- to 2-cm margin was given around the target volume to the block edge; a 1.5-cm margin was used around the parenchymal component of the target; a 2-cm margin was used along the ventricular component. In the latter part of the study (after 2000), as the International Commission on Radiation Units and Measurements guidelines began to be uniformly applied, this margin was equated to the following: GTV as defined above; the clinical treatment volume (CTV) as the GTV + approximately 1 cm (ventricular) and 0.5 (parenchymal); the planning target volume (PTV) as the CTV + 0.5 cm. In these cases, the distance from "the target volume" (PTV) block edge remained the same as for those patients treated before 2000. The patient with the pineal tumor and DI with no evidence for involvement of the suprasellar region was treated focally to only the pineal region (patient 2).

Dose

Six of the eight patients were treated to a dose of 30.6 Gy; the remaining two were treated to a dose of 36 Gy (see Table 1). In all the cases the target volume (labeled PTV after 2000) was encompassed by no less than the 95% isodose curve.

RESULTS

Survival

With a median follow-up of 57 months, the crude and actuarial survival rates are 100%. All patients are alive with no evidence of disease.

Local Control

Patterns of failure were determined by comparing the MRI obtained at the time of failure with the treatment portals and the MRI at the time of diagnosis. Two patients failed in the

CNS. One failure was a solitary nodule along the ventricle at the anterior part of the field block edge. The second failure included two sites that again were at the block edges (one at the anterior field edge [well posterior to the sella]) and one at the posterior field edge) along the ventricle. Both patients received a dose of 30.6 Gy. No failures occurred within the area receiving full dose, and no distant failures (spine) occurred. The 5-year actuarial CNS control rate was 71.4% (54.3–88.5%, 95% CI).

Salvage Therapy

Both patients who failed in the CNS were retreated with chemotherapy followed by cranial spinal irradiation to 19.8 Gy and 21.6 Gy. The sites of failure were boosted to a total dose of 36 Gy. Both patients remain alive and have no evidence of disease at 29 and 51 months from the time of recurrence.

Endocrinologic Outcome

As mentioned previously, five patients exhibited pituitary dysfunction at diagnosis. No further pituitary dysfunctions have occurred in any patient after radiotherapy to date.

DISCUSSION

The treatment of pure CNS germinomas in children remains controversial. Recently reported series suggest that treatment of children with cranial spinal irradiation results in excellent outcomes.[1,6,9,20] The side effects of such treatment, however, are of some concern, particularly for younger patients,[21,22] and include potential neurocognitive deficits, further pituitary dysfunction, and secondary malignancies. In an effort to reduce potential treatment-related side effects, combined modality therapy using CDDP-based chemotherapy regimens with reduced volume and dose irradiation have been examined. Those results have been encouraging, with the largest European clinical trials showing a 9% to 14% local failure rate and a salvage rate of over 50%.[10,13,16] The pattern of failure in both the European studies[13,16] showed a clear predominance of ventricular subependymal dissemination as the primary site of failure (7/9 failures and 3/4 failures, respectively), leading the study groups to consider widening the treatment volume to include the whole ventricular system.[13] Shirato et al[19] also reported marginal and distant ventricular failures with the use of 24-Gy focal irradiation after chemotherapy in 18 patients with solitary tumors and suggested that the smallest target volume should include the whole ventricular system.

The patterns of failure in our study (marginal relapses) are consistent with these studies and suggest that the current regimens of chemotherapy are not adequate in 10% to 15% of patients to completely sterilize the ventricular CSF. That no failures occurred in regions that received full dose suggests that a dose reduction to 30.6 Gy does not compromise local control. Aoyama et al[15] reported on 10 patients with solitary pure germinomas and normal β-HCG levels who were treated with focal irradiation after chemotherapy induction. One of those patients failed treatment, which was described as "outside the treated volume" intracranial with simultaneous spine metastases. Upon further review of the treatment fields,[19] an "inadequate (<1.5 cm) margin" was associated with an increased failure rate in six patients treated in that study (6/18 solitary, pure germinomas). However, only one of those six patients had a normal β-HCG level, which makes these results comparable to the European trials and our study[13,16] for patients with normal β-HCG levels and solitary, pure germinomas. The failure pattern in our patients was marginal in both cases with margins as described previously.

These studies, as well as this report, suggest that a reduction in dose and volume of irradiation after induction chemotherapy retains the excellent survival rates reported in other series, even though CNS failure rates are higher. Although our study suffers from a limited number of patients, it suggests, as do the previously cited studies, that one must anticipate a higher rate of failure with this approach when compared with regimens using irradiation to higher doses as the sole treatment modality. It should be anticipated that approximately 10% to 15% of patients will have ventricular failures and require further chemotherapy and/or irradiation using the current chemotherapy regimens. Whether the potential reduction of deleterious effects from whole ventricular irradiation, in a population that has largely achieved brain maturation, is worth the risk of a higher local failure rate remains to be determined.

Salvage of patients who recur using a combined modality approach is feasible. However, these patients will be exposed to higher doses of both radiotherapy and chemotherapy and the potential long-term complications of both modalities than patients treated with irradiation alone.

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