Primary Chemotherapy for Intracranial Nongerminomatous Germ Cell Tumors: Results of the Second International CNS Germ Cell Study Group Protocol

Stewart J Kellie, Hayden Boyce, Ira J Dunkel, Blanca Diez, Marc Rosenblum, Lynette Brualdi, and Jonathan L Finlay

ABSTRACT

Purpose
The optimum therapy for intracranial nongerminomatous germ cell tumors (NGGCT) remains controversial. The primary objective of this study was to determine whether intensive cisplatin and cyclophosphamide-based combination chemotherapy was effective in patients with intracranial NGGCT.

Patients and Methods
Twenty patients were enrolled, aged 5 to 41 years (median, 13 years). Initial therapy included two courses of Regimen A (cisplatin, etoposide, cyclophosphamide, and bleomycin). Patients achieving a complete remission (CR) then received two courses of Regimen B (carboplatin, etoposide, and bleomycin). Those in CR after four courses of treatment received one additional course of Regimen A and Regimen B, while those not in CR after four treatment courses underwent second-look surgery and/or irradiation.

Results
Sixteen of 17 patients assessable for response after two courses of treatment achieved a CR or partial response (CR/partial response, 0.94; 95% CI, 0.73 to 1.0). With a median follow-up of 6.3 years, 14 of 20 patients are alive without disease; eight patients were without relapse or progression, of whom three received local irradiation in first complete remission in violation of protocol, and six patients were in durable second or third complete remission after further chemotherapy and/or irradiation. The 5-year overall survival and event-free survival were 0.75 (95% CI, 0.56 to 0.94) and 0.36 (95% CI, 0.13 to 0.59), respectively.

Conclusion
Intensive chemotherapy was effective in one-third of patients in this study. Salvage therapy, including irradiation, was feasible in patients with recurrent disease.

INTRODUCTION

Germ cell tumors constitute less than 5% of all intracranial malignancies in patients aged less than 20 years residing in the Western hemisphere, and up to 12% in Japan [1,2]. Approximately 50% to 65% of CNS germ cell tumors are germinomas [3]. The remainder comprise a heterogeneous group of tumors collectively termed nongerminomatous germ cell tumors (NGGCT) which include pure or mixed populations of primitive germ cell elements including embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, malignant teratoma with or without features of classic germinoma, or mature or immature teratoma. It is common for several of these elements to be found within a single tumor specimen, and these mixed tumors are more common than pure forms [4,5]. These germ cell tumor populations are identical to their systemic counterparts histologically, ultrastructurally, and histochemically [4,6].

In a recent Japanese report of 153 histologically verified CNS germ cell tumors,
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36% were found to be pure germinomas; germinomas with syncytiotrophoblastic elements constituted 5%, mixed tumors in 32%, mature teratomas in 13%, teratomas with immature or malignant elements in 7%, pure embryonal carcinomas in 3%, pure choriocarcinomas in 2%, and pure yolk sac (endodermal sinus tumors) in 2% [7].

CNS germ cell tumors are typically found in midline sites, particularly the pineal and suprasellar regions. In 1997, Matsutani et al [7] described tumor location in 98 patients with NGGCT. The tumors were located in the pineal region (56%), the neurohypophysis (28%), basal ganglia (2%), and other sites, including cerebellopontine angle, lateral ventricle, and corpus callosum (9%). Five percent of tumors were located in multiple sites. A significant relationship between histopathology and location, age, or sex has not been demonstrated [4,7].

In contrast, the relationship between histopathology and patient outcome has been well described [2,3,7,8]. Matsutani et al [8] reported that patients with pure malignant NGGCT (embryonal carcinoma, yolk sac tumor, or choriocarcinoma) had a 3-year survival of 27%. Patients with mixed germinoma and teratoma (mature or immature) had a 3-year survival of 94%; patients with predominantly germinoma or teratoma mixed with other NGGCT elements had a 70% 3-year survival, and patients with mixed tumors composed of predominantly malignant NGGCT elements had a 3-year survival of 9%.

NGGCTs arising in the CNS are relatively radioreistant and associated with a relatively poor outcome, ranging from 20% to 45% survival following treatment with full-dose neuraxis radiation therapy alone [2,3,9]. The combination of radiation therapy with platinum-containing chemotherapy has been associated with improved outcomes [10-19].

Cranial or neuraxis radiation therapy is associated with significant neurodevelopmental, neuroendocrine, and somatic growth impairments in children [20-25]. Careful serial neuropsychologic testing in adults treated with cranial radiation therapy also demonstrates the development of late cognitive sequelae [26]. Both adults and children receiving cranial irradiation remain at risk of developing secondary tumors with a 20-year cumulative incidence of approximately 12% [27].

The Second International CNS Germ Cell Tumor Study Group protocol opened in 1994. The principal goal of the study was to improve the overall and progression-free survival of patients with NGGCT by intensifying a primary chemotherapy regimen, used previously by our group, by adding intensive cisplatin and high-dose cyclophosphamide in addition to etoposide and bleomycin to the induction regimen. The study aimed to avoid the use of radiation therapy among patients achieving a complete response to chemotherapy, assessed radiologically, by tumor markers and/or by second-look surgery.

### Patients and Methods

#### Eligibility

Eligibility criteria for enrollment on the study were: (1) pathologically proven CNS NGGCT with malignant elements and/or a CSF alpha-fetoprotein (AFP) > 10 U/mL and/or serum or CSF human chorionic gonadotrophin (HCG) > 50 mIU/mL in a patient without surgical biopsy confirmation but with magnetic resonance imaging (MRI) evidence of a pineal or suprasellar mass, (2) no prior chemotherapy or radiation therapy, (3) CSF cytology examination and MRI spine in the perioperative period, and (4) informed consent from patient or legal guardian and a copy of the signed consent form logged at the Study Operations Office (New York University, New York, NY). Values of HCG < 5 mIU/mL and AFP < 10 U/mL were considered normal. Neurosurgical guidelines provided opportunity for intraoperative CSF or perioperative sampling in patients for whom preoperative spinal tap was contraindicated.

#### Treatment

The treatment schema is outlined in Figure 1 and Table 1. Partial resection represented more than 10% but less than 50% removal of tumor, subtotal resection represented 50% to less than 90%, and radical (near total) resection more than 90% but less than 100% of the tumor mass. Gross total resection represented no visible tumor confirmed by postoperative gadolinium-enhanced MRI scan. Radiologically assessable disease was defined as disease at any site measuring more than 1.5 cm².

#### Assessment of Response

Response to chemotherapy was graded on the basis of neuroimaging findings and changes in abnormal AFP and/or HCG concentrations. Measurable disease in the primary site and/or neuraxis or extra-axial dissemination was compared before and after the first two courses of chemotherapy. Responses were categorized as: (1) complete response (CR) with total resolution of all radiographic and/or tumor markers, (2) partial response (PR) with at least 50% reduction in the area of the tumor (based on the product of maximal perpendicular diameters at the plane of greatest tumor area) with evidence of CSF/serum AFP and/or HCG elevations if previously raised, but at reduced levels compared with pretreatment levels, (3) stable disease (SD) with less than 50% reduction in tumor area or no more than 25% increase in tumor area with stable or improving tumor markers, and (4) progressive disease with more than a 25% decrease in tumor area.

#### Toxicity Assessment

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.

#### Statistical Analysis

Event-free survival (EFS) was defined as the time to first disease progression, disease recurrence, or death from any cause. Three patients who received local irradiation in first complete remission in violation of protocol were censored at the time of irradiation. Overall survival (OS) was measured from diagnosis to death from any cause or last follow-up visit. The log-rank test was used to compare event-free survival and overall survival with prognostic factors including age, tumor location (suprasellar vs pineal vs other), AFP and HCG elevation, and response to two courses of therapy [28]. Ninety-five percent confidence intervals were calculated using EpiInfo6 (Centers for Disease Control and Prevention, Atlanta, GA) [29].

#### Ethical Considerations

The study was approved by the institutional review board or equivalent committee at each participating institution. Each patient signed an informed consent.

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patient or guardian provided signed informed consent and these forms were reviewed centrally before individual enrollment on study.

**RESULTS**

**Patient Characteristics**

Twenty patients with NGGCT were enrolled between February 1995 and May 1997. Their characteristics are documented in Table 2. There were 17 males and three females. Their ages ranged from 5 to 41 years, with a median of 13 years.

**Surgery, Histopathology, and Diagnostic Markers**

Histopathology at diagnosis was available in 14 of 20 patients. Each of the 14 patients had evidence of malignancy. Of these, 11 patients had histopathologic evidence of mixed germ cell elements comprising varying combinations of nongerminomatous germ cell tumors, mature or immature teratoma and, in some cases, typical germinoma. Seven patients had near or gross total resections, one patient had subtotal resection, four patients had partial resection, and two patients had a biopsy. The six patients without histopathologic diagnoses had unequivocal elevations of serum AFP or HCG or both (Table 2).

**Response to Two Courses of Regimen A**

The response to two courses of Regimen A was determined in 17 of 20 patients. No data were available from two patients and another died from treatment-related toxicity during course 1. Eight of 13 patients assessed by MRI scanning achieved a radiologic CR, four patients demonstrated a PR, and one patient had SD. Of the 15 patients assessable by

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**Table 1. Chemotherapy Regimens**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Regimen A</th>
<th>Regimen B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>105 mg/m²</td>
<td>Carboplatin (AUC = 7)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150 mg/m²</td>
<td>Etoposide 150 mg/m²</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2gm/m²</td>
<td>Carboplatin (AUC = 7)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150 mg/m²</td>
<td>Etoposide 150 mg/m²</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2gm/m²</td>
<td>Etoposide 150 mg/m²</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150 mg/m²</td>
<td>Bleomycin 15 mg/m²</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>15 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the curve.

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**Fig 1.** Treatment outline. EOD, extent of disease; XRT, radiation therapy.
Chemotherapy for Intracranial NGGCT

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Histopathology</th>
<th>Location</th>
<th>AFP ng/ml (Serum/CSF)</th>
<th>HCG mU/ml (Serum/CSF)</th>
<th>Pattern of Relapse</th>
<th>Current Status (months)</th>
<th>EFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>M</td>
<td>Mixed GCT w/T, YST</td>
<td>P, S</td>
<td>638/336 374/1,111</td>
<td>80/500</td>
<td>No</td>
<td>Diffuse DOD</td>
<td>5</td>
<td>8</td>
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<tr>
<td>2</td>
<td>12</td>
<td>M</td>
<td>Mixed GCT w/T, YST</td>
<td>P</td>
<td>12/1150 142/499</td>
<td>78/508</td>
<td>—</td>
<td>Local CR1 62+</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>YST</td>
<td>P</td>
<td>325/338 78/508</td>
<td>116/162</td>
<td>—</td>
<td>Local CR1 62+</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>M</td>
<td>—</td>
<td>P, S</td>
<td>298/338 127/436</td>
<td>16/127</td>
<td>—</td>
<td>No</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>M</td>
<td>—</td>
<td>S</td>
<td>169/99 7/127</td>
<td>370/1,240</td>
<td>No</td>
<td>CR1 76+</td>
<td>13</td>
<td>18</td>
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<tr>
<td>6</td>
<td>15</td>
<td>M</td>
<td>Mixed GCT w/EC, YST</td>
<td>P</td>
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<td>370/1,240</td>
<td>No</td>
<td>CR1 76+</td>
<td>13</td>
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<td>169/99 7/127</td>
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<td>No</td>
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<td>F</td>
<td>Mixed GCT w/EC, EDST, G</td>
<td>P</td>
<td>169/99 7/127</td>
<td>370/1,240</td>
<td>No</td>
<td>CR1 76+</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>F</td>
<td>Mixed GCT w/EC, EDST, G</td>
<td>P</td>
<td>169/99 7/127</td>
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<td>No</td>
<td>CR1 76+</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

Outcome

With a median follow-up time of all patients of 6.3 years, 14 of 20 patients (0.7) are alive from 38+ to 86+ months from diagnosis, including eight in first complete remission (Fig 2). Three patients received radiation therapy in protocol violation in first complete remission (patients 3, 11, and 14). Eleven patients have relapsed or progressed 4 to 70 months (median, 13 months) from diagnosis. The 5-year OS for the study population was 0.75 (95% CI, 0.56 to 0.94) and the EFS was 0.36 (95% CI, 0.13 to 0.59; Fig 3).

Prognostic Factors

Raised tumor markers. Nine patients had perioperative HCG values > 100 mU/mL in serum, CSF, or both. Two patients, including one treated with radiation therapy in violation of protocol, remain in first complete remission. Four are alive in second complete remission, three died of disease, and one died from toxicity of treatment in course 1. Two additional patients with histologically proven mixed germ cell tumors and raised AFP levels also had abnormal HCG levels in CSF or plasma, but less than 50 mU/mL. Both of these patients (patients 9 and 13) are long-term survivors in first complete remission. Another patient (patient 19) had only germinoma identified histologically after partial resection; however, preoperative AFP and HCG were elevated beyond the normal range. He remains in first complete remission at 77+ months. Overall, nine (75%) of 12 patients with an elevated HCG at diagnosis remain in long-term durable remissions.

We examined the relationship between higher levels (> 1,000) of AFP and/or HCG and outcome. Of eight patients in this category, four remain in first complete remission, three died of disease, and one died from therapy-related toxicity. We could not identify a relationship

AFP and HCG concentrations, 13 of 15 demonstrated normalization of AFP and/or HCG with improvement in the remaining two patients. Four patients with normalization of AFP and/or HCG had MRI assessments of PR or SD, suggesting the presence of residual mature or immature teratoma. Of the 17 patients evaluated after course 2, 11 patients achieved CR, five patients had a PR (CR + PR = 0.94; 95% CI, 0.73 to 1.0), and one patient had SD. Excluding three patients who received full-dose local irradiation in first complete remission in violation of protocol and another who died of toxicity during the first complete response, two patients, including one treated with radiation therapy, remain in first complete remission. Another patient (patient 19) had only germinoma identified histologically after partial resection; however, preoperative AFP and HCG were elevated beyond the normal range. He remains in first complete remission at 77+ months. Overall, nine (75%) of 12 patients with an elevated HCG at diagnosis remain in long-term durable remissions.

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between raised AFP and/or HCG or the highest recorded levels of these tumor markers in the pretreatment period and outcome.

**Extent of Initial Surgery**

We could not demonstrate any prognostic significance related to extent of initial surgery. Eight children had no surgery or biopsy only, five had partial or subtotal resections, and seven had near total resections. The proportion of long-term survivors in durable first or subsequent remission was similar in each group (0.62 v 0.8 v 0.71, respectively).

**Response to Two Courses of Regimen A**

Of the 17 patients assessable for response to two courses of Regimen A, eleven patients achieved a CR to two courses of regimen A and five achieved a PR. The median EFS for each group was 62 versus 23 months, and for OS, 75 versus 41 months, respectively.

**Patterns of Relapse**

Eleven patients with NGGCT relapsed based on neuraxis imaging in nine patients, markers in one patient, and no information in one deceased patient. Of the patients with imaging data available, seven (78%) of nine had evidence of leptomeningeal or distant metastases, and two of nine had recurrence localized to the primary site. Six of 11 relapsing patients, including three of seven patients with disseminated recurrence, remain free of disease 18, 33, 50, 52, 57, and 67 months from first relapse after treatment with standard-dose cranial or craniospinal irradiation in each survivor and high-dose chemotherapy comprising high-dose thiotepa or high-dose cyclophosphamide with autologous stem-cell transplant in three patients. Imaging information about pattern of relapse was available in five of seven patients with elevated HCG at diagnosis. Four of the five had diffuse leptomeningeal disease at relapse, including two (patients 12 and 20) who were successfully retreated.

**Toxicity**

Chemotherapy in this study was associated with moderate to severe toxicity in most patients. The interval between courses increased from 21 days for course 1 (range, 14 to 50 days) to 28 days (range, 17 to 46 days) for course 4. The number of days in hospital was influenced by local practice with a median of 5 days during course 1 (range, 5 to 22 days) and a median of 4 days in course 4 (range, 5 to 16 days). Of all assessable treatment courses, thrombocytopenia (platelets ≤ 20 × 10^9/L) and neutropenia (neutrophils ≤ 0.5 × 10^9/L) developed in 64% and 81% of assessable courses, respectively. Platelet transfusions, RBC transfusions, and admissions for fever associated with neutropenia were required in 81%, 61%, and 56% of courses, respectively. Positive blood cultures were documented in two patients, one patient, two patients, and one patient in each of the first four treatment courses, respectively. One patient died from toxicity. This patient (patient 15) developed bacterial and fungal sepsis, thrombotic thrombocytopenic purpura, and renal failure during course 1, resulting in death.

Therapy was modified because of toxicity in seven patients. Bleomycin was omitted from one or more courses in four patients because of declining pulmonary function, and
cisplatin was omitted from one course in patient 1. The parents of patient 12 requested no further protocol chemotherapy after course 1. Four of these six patients died of disease at 5, 6, 10, and 76 months from diagnosis. Another (patient 13) was removed from study after course 3 at parental request because of seizures. He received no further therapy and remains in first complete remission at 80+ months from diagnosis.

Toxicities recorded at late follow-up were predominantly related to panhypopituitarism and/or diabetes insipidus secondary to the impact of primary tumor. One patient (patient 14) had evidence of a persisting bitemporal hemianopsia evident from initial presentation. She also had evidence of frontal lobe necrosis and learning difficulties, possibly as a consequence of local irradiation delivered in first complete remission. Mild pulmonary function abnormalities were common. Mild high-frequency hearing loss without the need for aids was common in surviving patients.

**DISCUSSION**

The efficacy of cisplatin-containing combination chemotherapy for newly diagnosed or refractory gonadal and extracranial germ cell tumors has been recognized since the late 1970s and early 1980s [30,31]. Intracranial NGGCT appeared to be a logical candidate in which to study combination chemotherapy. The first reported trial involving cisplatin, etoposide, and bleomycin for newly diagnosed intracranial NGGCT was conducted in Japan between 1983 and 1985 and reported in the Japanese language by Matsukado. Chemotherapy was given after irradiation [32]. The 2-year OS of the 30 patients was 68%, and compared favorably with the median survival of 18 months in 33 patients with NGGCTs reported by the Japanese Intracranial Germ Cell Tumor Study Group who received only postoperative irradiation [32].

The results of our study compare favorably to comparable groups of patients published by Japanese investigators. All patients in our study had histologic and/or tumor marker evidence of elements of embryonal carcinoma, yolk sac tumor, or choriocarcinoma. The outcome of comparable patients reported by Sawamura et al [33] treated with radiation therapy, and in some cases chemotherapy before or after recurrence, was a 5-year and 10-year survival of 38% and 25%, respectively, among patients with germ cell tumors with a highly malignant component.

Matsutani et al [32] divided patients into good, intermediate, and poor prognosis groups. All patients received radiation therapy and chemotherapy either before or after radiation therapy composed of carboplatin/cisplatin and etoposide in intermediate prognosis patients, or similar treatment combined with ifosfamide in the poor prognosis groups. With a median follow-up of less than 3 years, the intermediate prognosis group had a tumor-free rate of 56% and four of the nine poor prognosis group patients died within 10 months of diagnosis, including three patients treated on the ifosfamide-containing arm who progressed during preradiation chemotherapy. In comparison, the majority of patients in our study would have been classified as poor prognosis in the Japanese experience, but have demonstrated a satisfactory outcome, noting the absence of radiation therapy in five of our 14 long-term survivors.

The efficacy of platinum-containing combination chemotherapy in the treatment of intracranial germ cell tumors is well established; however, the choice of drugs, particularly carboplatin versus cisplatin, and the efficacy of bleomycin, have been the subjects of ongoing study [10-16,32-36].

The therapeutic impact of radiation therapy in patients with intracranial NGGCT has not been clearly defined. A review of European treatment experience by Calaminus et al [17] showed a limited sensitivity of NGGCT to radiation doses exceeding 50 Gy. Treatment of intracranial NGGCT with neuraxis irradiation alone has been associated with a relatively poor long-term outcome, ranging from 20% to 45% [2,3,9].

The late sequelae of radiation therapy to the CNS, particularly the adverse somatic growth effects, hearing loss, neuropsychological and cognitive impairments, neuro-endocrine disorders, and risks of secondary cancers are well described [21,22,26,27,37] and the observation of durable responses of extracranial NGGCT to chemotherapy without radiation therapy prompted an earlier trial of primary chemotherapy in children and young adults with intracranial NGGCT [36].

We recognized that the extent of these irradiation-associated sequelae may be less marked than those seen in much younger patients receiving craniospinal axis irradiation; however, cranial irradiation was found to be positively associated with impaired quality of life in our First International Study (FIS). The median age at diagnosis of CNS NGGCT in the FIS was 10.1 years compared to 13 years in the current study. The 2-year survival of 26 patients with NGGCT in the FIS was 0.62; however, approximately half of the study population received radiation therapy, mostly at the time of recurrence or progression [36].

The second study of International CNS Germ Cell Study Group built on the experience of the group’s first study and the work of others. In summary, the chemotherapy differences were the intensification of the first two courses of therapy with the substitution of cisplatin for carboplatin and the addition of high-dose cyclophosphamide and secondly, the provision of a fifth and sixth course of therapy in patients achieving a complete response after four courses of therapy.

The rationale for substituting cisplatin for carboplatin was based on the observation that carboplatin was less effective than cisplatin at equivalent doses in two-drug and three-drug treatment protocols in patients with non-CNS...
germ cell tumors [17,38,39]. We speculated that differences in the efficacy of these two platinum drugs may be a factor contributing to the differences reported among patients with intracranial NGGCT.

The addition of cyclophosphamide was based on the observation in the FIS that all 10 patients who received cyclophosphamide at first progression or recurrence achieved a CR [36]. Moreover, the addition of cyclophosphamide to an intensive carboplatin-containing regimen could be expected to be significantly myelotoxic. In addition, the Second Internatinal Study (SIS) alternated the cisplatin-containing regimen with the carboplatin-intensified regimen used in the first study [36] (carboplatin at 500 mg/m²/d x 2 days compared with cisplatin 105 mg/m²/d) because of the high response rate observed in the first study.

The OS of patients with CNS NGGCT in the SIS is at least comparable to the FIS (SIS 5-year OS, 0.75; 95% CI, 0.56 to 0.94; FIS 2-year OS 0.62; SD not available). Approximately half of the patients remain free of progression or relapse in both the FIS and SIS (measured at 2 years in the FIS and at a median follow-up of 6.3 years in the SIS); however, only one of 19 patients died from toxicity in the SIS compared to five of 26 patients with NGGCT dying from causes other than disease in the FIS. Robertson et al [19] treated 18 patients with intracranial NGGCT with irradiation and three or four cycles of cisplatin and etoposide. Their study reported 4-year EFS of 67% and total survival of 74%. The median age in their study was 11 years and all but one patient (aged 4 years) completing chemotherapy received more than 50 Gy involved field radiation therapy and whole brain or craniospinal radiation therapy in six patients [19]. Survival after recurrence or progression was very brief. The longest survival recorded after treatment failure was only 4 months and this observation is relevant to the interpretation of the OS statistic [19].

Two patients who achieved a CR after two courses of therapy in the SIS received local cranial radiation therapy in violation of the protocol, and a third received local radiation therapy for a residual mass after four courses of therapy. Each of these patients remains in first complete remission at 62+, 75+, and 55+ months from diagnosis, respectively. Overall, nine of 14 surviving patients received radiation therapy and remain in durable first or subsequent remissions.

The results of long-term quality of life and neuropsychologic function testing of patients enrolled in the SIS will be the subject of a separate report. We studied this aspect of late outcome in survivors of the FIS and demonstrated an increased risk of adverse quality of life and neuropsychologic functioning in younger patients, patients with CNS NGGCT (compared to CNS germinomas), and in patients treated with radiation therapy [40]. Parents of children 18 years and younger at the time of testing (median, 6.1 years after diagnosis) who received irradiation reported significantly lower self-esteem in addition to limitations in their roles at school and with friends because of emotional or behavioral problems [40].

Biologic studies examining the relationship between ploidy [41,42], cytogenetic abnormalities, or other molecular markers and clinical outcome are warranted and may assist in the identification of the one-third or more of patients with NGGCT who may be cured with chemotherapy alone or assist in the assessment of prognosis at diagnosis [43-45]. Potential relationships between biologic prognostic factors and treatment modality with the degree of elevation of diagnostic tumor markers, their rate of decline, or the rapidity of achieving CR with long-term outcome remain to be determined.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.
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