Brain Metastases and Testicular Tumors: Need for Aggressive Therapy

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In late 1974, the combination of cisplatin, vinblastine, and bleomycin (PVB) became the standard chemotherapeutic regimen for treatment of disseminated nonseminomatous germ cell testicular tumors (NSGCT) at Indiana University Hospital. A retrospective analysis of the treatment records of all patients with brain metastases from NSGCTs treated at the Indiana University Radiation Oncology Department from 1975 through 1982 was undertaken. These 22 patients were divided into four groups. Group 1 (n = 5) consisted of those patients who presented initially with brain metastases and had no prior systemic treatment. Group 2 (n = 4) were referred to Indiana University after failing systemic therapy other than PVB chemotherapy. Group 3 (n = 5) consisted of those patients who after achieving a complete response with PVB developed a relapse confined to the brain. Group 4 (n = 8) consisted of those patients who were initially treated with PVB and eventually developed progressive disease and brain metastases. The survival by group is 80%, 0%, 60%, and 0%, respectively, with the overall survival for the entire group being 31.8%. All patients currently alive have a range of follow-up of 22 to 96 months from diagnosis and 12 to 83 months from whole brain irradiation (WBRT). Group 1 was treated with PVB +/- doxorubicin plus WBRT. Group 3 was treated with surgical excision, when feasible, followed by WBRT and platinum-containing chemotherapy. Group 2 and 4 were usually treated with palliative intent WBRT. The CNS is a site of sanctuary from PVB. Patients with brain metastases who may achieve a complete response should be treated with curative intent and receive aggressive WBRT (5,000 rad/25 fractions) with concomitant chemotherapy. J Clin Oncol 2:1397-1403. © 1984 by American Society of Clinical Oncology.

Prior to the introduction of the chemotherapeutic combination of cis-diammine-dichloroplatinum, vinblastine, and bleomycin (PVB), patients with disseminated nonseminomatous germ cell testicular tumors (NSGCTs) had a grave prognosis with as much as 80% to 90% mortality.1,2 Beginning in August 1974, PVB chemotherapy became the standard chemotherapeutic regimen for the treatment of disseminated NSGCTs at Indiana University Hospital. Since its introduction at Indiana University, numerous clinical trials have been performed.3-5 These trials have proven that PVB is an effective systemic treatment of NSGCTs with a 70% complete response (CR) rate, and most of these CRs have been durable.

As with other chemosensitive malignancies, the discovery of sanctuary sites for NSGCTs became evident. Like leukemia, certain lymphomas, and small-cell lung carcinoma, the CNS was revealed as a site of sanctuary from PVB. With this fact and the question of whether a patient who presents with disseminated NSGCT involving the brain is curable, a retrospective review was undertaken to study all patients with brain metastasis from NSGCTs treated at the Indiana University Radiation Oncology Department from 1975 through 1982.

Patients and Methods

Twenty-two patients were identified with brain metastases from NSGCTs that were treated in the Indiana University Radiation Oncology Department from 1975 through 1982. No patients with brain metastases seen during this time were excluded.

These 22 patients were retrospectively divided into four groups. Group 1 (n = 5) were those patients who presented with brain metastases and had no prior systemic therapy. Group 2 (n = 4) were those patients that were referred to Indiana University after failing systemic therapy other than PVB chemotherapy. Group 3 (n = 5) were those patients who after achieving a CR with PVB developed a relapse confined to the brain. Group 4 (n = 8) were those patients who were initially treated...
with PVB and eventually developed progressive disease and brain metastases.

A CR was defined as a complete disappearance of all clinical, radiographic, and biochemical evidence of disease. A partial response (PR) was a decrease of 50% or more in the sum of the products of diameters of all measurable lesions.

All radiation therapy treatments were delivered with Picker C/9 Cobalt 60 teletherapy (Picker, Cleveland) or a Varian Clinac 4 meV linear accelerator (Varian Associates, Palo Alto, Calif). In our discussion of response to whole brain irradiation (WBRT), those patients dying during treatment or within one month of completing WBRT are assumed not to have gained control of their brain metastasis.

**Group 1 (n = 5)**

The average age at diagnosis was 23 years. Four patients presented as stage III; one patient presented as a stage I and was treated with radical orchectomy and received no other treatment until his referral to Indiana University with disseminated disease. All brain metastases were proven by either brain scan or head computed tomographic (CT) scan. Three patients had a solitary brain metastasis, and two had multiple lesions. All patients had systemic metastatic disease involving the lungs and retroperitoneum at presentation. The pathologic diagnosis was immature teratoma (one), embryonal (one), choriocarcinoma (one), and embryonal plus choriocarcinoma (two).

**Group 2 (n = 4)**

The average age at diagnosis was 32 years. At initial presentation, two patients were stage II, one was stage III, and one was an extragonadal mediastinal presentation. All were referred with progressive disease and had received prior chemotherapy. All had received actinomycin D either as a single agent or in combination with other agents. Two received vinblastine and bleomycin; one received cytoxan, vincristine, and methotrexate; one received mithramycin, and one received nitrogen mustard. Three had retroperitoneal node dissections (RPND) before referral, and one had pelvic/paraortic irradiation before referral. Three patients developed brain metastases after beginning platinum-containing chemotherapy, and none were in a peripheral CR. One had brain metastases at the time of referral. The pathologic diagnosis was seminoma plus embryonal (one), teratocarcinoma plus embryonal (one), choriocarcinoma (one), and teratocarcinoma with elements of choriocarcinoma plus embryonal (one).

**Group 3 (n = 5)**

The average age at diagnosis was 28 years. Two patients presented with stage II disease, and three presented with stage III disease. Only one patient in this group had initial treatment at another institution, and he received several chemotherapeutic agents (actinomycin D, methotrexate, Leukeran [Burroughs Wellcome, Research Triangle Park, NC], vincristine, bleomycin, and Adriamycin [Adria Laboratories, Columbus, Ohio]) as well as undergoing a retroperitoneal node dissection followed by postoperative radiation therapy. All patients in this group were treated with PVB +/- A (Adriamycin) and eventually achieved a CR and then developed brain metastases as the sole site of relapse. The pathologic diagnosis was embryonal (two), embryonal with foci of seminoma (one), embryonal with yolk sac elements (one), and embryonal with trophoblastic differentiation (one).

**Group 4 (n = 8)**

The average age at diagnosis was 27 years. All patients in this group presented with advanced disease. Five had extragonadal presentations with four being retroperitoneal and one being mediastinal. Three patients were stage III. All were initially treated at Indiana University with PVB +/- A. Eventually they all developed progressive disease and brain metastases. The pathologic diagnosis was embryonal (one), embryonal plus yolk sac (one), presumed choriocarcinoma (three), mixed without choriocarcinoma (one), and mixed with choriocarcinoma (two).

**TREATMENT AND RESULTS**

All patients who were eligible were treated on various prospective randomized studies involving different dosages of PVB +/- A. These studies and their results have been described elsewhere.3-5

All patients with brain metastases were treated with curative-intent WBRT if there was any chance of achieving a CR with chemotherapy. Because of the changing policy throughout this time period, various radiation treatment schedules were used.

**Group 1**

Since this group of patients presented with markedly advanced disease, they were treated immediately with aggressive PVB +/- A. WBRT was begun as soon as possible, usually during the first course of induction chemotherapy (Table 1). All four patients who have survived attained control of their brain metastases. One patient underwent a craniotomy to rule out recurrence, and only a necrotic cystic lesion was found. This patient had received the larger dose per fraction of 3,300 rad in 11 fractions. The one patient who died was considered clinically to have new or recurrent brain metastasis (two months after completing WBRT) before his death; this patient also had progressive pulmonary disease having failed salvage chemotherapy. The overall survival of group 1 is at 80%. These patients have now survived 34 +, 48 +, 58 +, and 68 + months from diagnosis and 34 +, 48 +, 57 +, and 64 + months from day 1 of WBRT.

**Group 2**

Since this group of patients had been heavily pretreated with chemotherapy before referral,
appropriate dose modifications as well as drug deletions were performed for the individual patient.

All patients presented with progressive disease; only one presented with brain metastases. Two were treated with PVB + A × 4 as induction, one received PVB × 7, and one received platinum and Adriamycin initially. The one patient with brain metastases received concomitant WBRT of 4,700 rad in 21 fractions.

The average length of time to the development of brain metastases from diagnosis was 36.5 months (8, 11, 17, and 110 months). The one patient who developed brain metastases 110 months after diagnosis was initially treated in 1968 with orchiectomy, RPND, and two years of actinomycin D, and he did well for eight years. The patient developed brain metastases 20 months after diagnosis of its recurrence.

All patients achieved a PR after their platinum-containing induction chemotherapy. Patients in PR were followed closely and placed on maintenance chemotherapy, and when evidence of progression developed they were begun on salvage chemotherapy that has changed through the years of this review. The salvage therapy was usually a platinum-containing chemotherapy. One patient also underwent a RPND and thoracotomy in an attempt to resect residual disease. No patient attained CR with salvage therapy.

### Table 1. Treatment and Results of Patients in Group 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Histology</th>
<th>No. CNS Metastases</th>
<th>Therapy</th>
<th>Status (mo)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Immature teratoma</td>
<td>Multiple</td>
<td>PVB + A × 4, WBRT 5,000 rad 25 fx, PB and VP-16 × 4 orchiectomy RPND and thoracotomy</td>
<td>CR alive</td>
<td>34 +</td>
</tr>
<tr>
<td>2</td>
<td>Choriocarcinoma</td>
<td>Solitary</td>
<td>PVB + A × 4, WBRT 3,300 rad 11 fx, P and VP-16 × 2 orchiectomy craniotomy</td>
<td>PR alive</td>
<td>48 +</td>
</tr>
<tr>
<td>3</td>
<td>Embryonal and choriocarcinoma</td>
<td>Multiple</td>
<td>PVB × 7, WBRT 5,000 rad 24 fx, orchiectomy Adriamycin, CMF</td>
<td>Dead with disease</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Choriocarcinoma and embryonal</td>
<td>Solitary</td>
<td>Orchiectomy, PVB + A × 4 WBRT 5,000 rad 25 fx</td>
<td>CR alive</td>
<td>58 +</td>
</tr>
<tr>
<td>5</td>
<td>Embryonal</td>
<td>Multiple</td>
<td>Orchiectomy PVB × 4, WBRT 5,000 rad 25 fx, lumbar spine RT 4,200 rad 20 fx</td>
<td>CR alive</td>
<td>68 +</td>
</tr>
</tbody>
</table>

**NOTE.** fx = Fraction.
Two patients failed to complete their planned course of WBRT; both died while under treatment. Both patients who completed their planned course of WBRT had good control of their brain metastases. Before the patients’ deaths from progressive systemic disease, no difficulties with the CNS were reported. The overall survival of group 2 is 0%. These patients survived 11, 17, 17, and 111 months from diagnosis and 0, 0, 3, and 7 months from the first day of WBRT.

Group 3

All patients in this group had achieved a CR and then developed a recurrence confined to the brain (Table 2). One of the two patients who died was diagnosed with carcinomatous meningitis two months after completing WBRT with no lesions seen on head CT scan; this patient probably had seeding of the meninges at the time of treatment of the solitary metastasis located in the left occipital region. A course of cranial spinal irradiation was given with a reduced dose to the brain; the patient died a short time after completing his cranial spinal irradiation. The other failure was secondary to recurrent tumor in the brain. A recurrence was found on head CT scan four months after completing postoperative WBRT. The patient died seven months after starting WBRT with no evidence of other disease except for rising serum markers and brain recurrence. This patient also did not receive any postoperative platinum-containing chemotherapy.

The overall survival of group 3 is 60% (3/5). The survival of those treated with excision fol-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Histology</th>
<th>Initial Therapy</th>
<th>Time From DX to Development CNS Mets (mo)</th>
<th>No. CNS Metastases</th>
<th>CNS Therapy</th>
<th>Survival Diagnosis CNS Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Embryonal and seminoma</td>
<td>Orchiectomy, PVB × 4</td>
<td>6</td>
<td>S</td>
<td>Craniotomy, WBRT 4,000 rad 20 fx, PB and VP-16 × 2</td>
<td>61 + 55 + CR</td>
</tr>
<tr>
<td>2</td>
<td>Embryonal with yolk sac elements</td>
<td>Orchiectomy, PVB × 3</td>
<td>13</td>
<td>M</td>
<td>WBRT 5,000 rad 25 fx, PVB × 2</td>
<td>96 + 86 + CR</td>
</tr>
<tr>
<td>3</td>
<td>Embryonal</td>
<td>Orchiectomy, RPN, PVB × 4, thoracotomy PB VP-16 × 3</td>
<td>19</td>
<td>S</td>
<td>Craniotomy, WBRT 3,000 rad 10 fx, P and VP-16 × 2, craniospinal irradiation (see text)</td>
<td>23 4 Dead with disease</td>
</tr>
<tr>
<td>4</td>
<td>Embryonal</td>
<td>Orchiectomy, PVB + A × 4, thoracotomy, and RPN, VP-16 × 2</td>
<td>10</td>
<td>S</td>
<td>Craniotomy, WBRT 4,000 rad 20 fx, P and VP-16 × 2</td>
<td>22 + 12 + CR</td>
</tr>
<tr>
<td>5</td>
<td>Embryonal with trophoblastic differentiation</td>
<td>Orchiectomy, RPN, pararaoortic XRT, AMC, VBA PB VP-16 × 7, thoracotomy</td>
<td>29</td>
<td>S</td>
<td>Craniotomy, WBRT 5,000 rad 25 fx</td>
<td>36 7 Dead with CNS disease alone</td>
</tr>
</tbody>
</table>

NOTE. S = solitary; M = multiple; AMC = actinomycin-D, methotrexate, and chlorambucil; VBA = vincristine, bleomycin, and Adriamycin; fx = fraction.
Brain metastases and testicular tumors

Followed by WBRT is 50% (2/4). These two patients have survived 22+ and 61+ months from diagnosis and 12+ and 55+ months from day 1 of WBRT. The one patient treated with WBRT alone is now alive 96+ months from diagnosis and 83+ months from beginning WBRT.

Group 4

The patients in this group were usually treated with palliative intent. Most had failed both first-line and second-line chemotherapy before developing brain metastases. All were initially treated with PVB +/- A. Six patients achieved a PR after their induction chemotherapy; two either had no response or progressive disease after induction chemotherapy.

Eventually all of these patients developed brain metastases while their systemic disease progressed. The average time to development of brain metastasis after diagnosis was 7 1/2 months (range, two to 27 months).

Overall, 50% (4/8) of the patients achieved good palliation of their brain metastases (only one developed recurrent brain metastases 12 months after beginning WBRT). Fifty percent (4/8) of the patients did not achieve good palliation of their brain metastases; three died either during their planned WBRT or within one month of completing WBRT. The other patient survived five months after his first course of WBRT; he developed a recurrence of new brain metastases four months after completing the first course of WBRT and was retreated through local ports to the brain (2,000 rad/five fractions). The patient died less than one month after completing WBRT.

The overall survival of group 4 is 0%. The average survival from diagnosis was 11.75 months (3, 4, 8, 12, 13, 18, and 28 months), and survival from the first day of WBRT was 4.3 months (< 1, < 1, < 1, 2, 4, 5, 9, and 13 months).

RESULTS BY RESPONSE TO THERAPY

The overall survival of all patients in this study was 31.8% (7/22). There was a total of eight patients who were considered to be a CR at some point during their therapy; their overall survival was 75% (6/8). A total of 12 patients were classified as a PR at some point during their therapy; their overall survival was 8.3% (1/12). Two patients showed no response to therapy; their overall survival was 0% (0/2) (Fig 1). In summary, seven of 22 patients are alive 22+, 34+, 48+, 58+, 61+, 68+, and 96+ months from diagnosis and 12+, 34+, 48+, 55+, 57+, 64+, and 83+ months from beginning WBRT.

DISCUSSION

Brain metastases are usually a sign of advanced disease in patients who have never received treatment or in those with progressive disease. Furthermore, the development of brain metastases in the patient who has achieved a CR is discouraging to both the patient and physician. The physician treating a patient with brain metastases as part of a disseminated disease process has usually only considered the patient as a candidate for palliation. Only patients with solitary brain metastasis after having achieved a CR for their initial primary have been considered curable.

The analysis of this data has allowed the identification of certain subgroups of patients who should be treated aggressively with curative intent. This is particularly true of patients who at initial diagnosis have brain metastases from disseminated disease. The results of the study show that 80% (4/5) of these patients are alive, and 100% of those who achieved a CR have survived. It should be re-emphasized that the minimum follow-up in this group is an impressive 34 months. These patients (group 1) should be treated aggressively with curative intent with WBRT (5,000 rad/25 fractions) and concomitant PVB. Though it is likely that significant therapeutic
levels of PVB do not cross the blood-brain barrier as evidenced by the five recurrences confined to the brain (group 3), the concomitant administration of WBRT and PVB may have an additive effect by allowing higher concentrations of PVB into the brain where it can enhance the effect of the WBRT.

The dose-response curve in the patient population in this study is not helpful in determining the optimal dose of WBRT. It is most likely that the higher dose per fraction that is often used for palliation is suboptimal as it could be expected to be associated with a higher degree of side effects especially when given in combination with chemotherapy. Patients with disseminated disease involving the brain did well with WBRT of 5,000 rad in 25 fraction during induction PVB, and we believe this to be the recommended dose of radiation for patients in this category. The only patients who had difficulty with acute side effects from concomitant WBRT and chemotherapy were those who received Adriamycin in addition to PVB as they developed a moderate to severe radiation dermatitis of the scalp. None of these patients has developed long-term visual or neuropsychologic disturbance secondary to therapy.

The patients who have solitary or multiple brain metastases with no other evidence of recurrent disease should be treated aggressively with curative intent. From our data, 60% (3/5) were able to again achieve a CR and to survive. The patient with a solitary brain recurrence after a chemotherapy-induced CR is treated with surgical excision followed by WBRT and platinum-containing chemotherapy. These patients are usually given two courses of chemotherapy since a CNS recurrence may herald a systemic relapse like meningeal leukemia in childhood acute lymphocytic leukemia. Our data show that 50% (2/4) again achieved a CR and survived with this approach, and one of the two patients who died (with carcinomatous meningitis) showed good control in the brain. The other patient who failed did not receive postoperative platinum-containing chemotherapy; he was the only patient identified to die solely with uncontrolled disease confined to the brain. Patients with multiple brain metastases as the only site of recurrence should be treated with curative intent and receive WBRT (5,000 rad/25 fractions) and concomitant platinum-containing chemotherapy. Our data show that one patient with multiple brain metastases is alive and well 83 months after beginning WBRT. The excellent treatment results — with those patients in group 1 and the one patient with multiple metastasis in group 3 — allow the alternative treatment plan of WBRT and platinum-containing chemotherapy for solitary brain metastasis that are located in areas carrying a high risk of severe long-term complications with surgical excision. Furthermore, this shows that the surgeon need not attempt complete excision if this may result in neurologic deficit.

In group 1, histologic tissue type did not affect survival because patients surviving had the following pathologic diagnosis: immature teratoma, embryonal, choriocarcinoma, and choriocarcinoma plus embryonal. The one patient who died with progressive systemic disease had a pathologic diagnosis of embryonal with elements of choriocarcinoma. The same is true for group 3 since the patients surviving had the pathologic diagnosis of embryonal, embryonal with foci of seminoma, and embryonal with yolk sac elements. The two patients who died had the diagnosis of embryonal and embryonal with trophoblastic differentiation.

We have previously examined patients with disseminated NSGCTs in an attempt to identify whether any subgroups would benefit from prophylactic cranial irradiation (PCI). Analysis of our data did not show that PCI would be of benefit. Further evidence that there is no role for PCI is that only approximately 2% of our patients develop brain metastases. It is recommended that patients who have widely disseminated disease involving the brain (group 1) should be treated aggressively with curative intent and receive WBRT of 5,000 rad in 25 fractions and concomitant PVB induction chemotherapy. Patients with recurrences confined to the brain that are solitary should receive surgical excision (if technically feasible) followed by WBRT of 4,500 to 5,000 rad in 22 to 25 fractions and concomitant platinum-containing chemotherapy. Patients with brain metastases and progressive systemic disease after salvage chemotherapy are not curable and should be treated palliatively.
BRAIN METASTASES AND TESTICULAR TUMORS

The retrospective analysis of the treatment results of patients with brain metastases in groups 1 and 3 clearly indicate that NSGCTs are not radioresistant. Moderate doses of radiation controlled disease and effected long-term survival. These data suggest that there may be an additive effect between radiation and platinum-containing chemotherapy on brain metastases.

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REFERENCES