Five-Year Survival of Patients With Disseminated Nonseminomatous Testicular Cancer Treated With Cisplatin, Vinblastine, and Bleomycin

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Ninety-one patients with disseminated testicular non-seminomas were treated with 3 to 4 cycles of cisplatin, vinblastine, and bleomycin (PVB) induction chemotherapy followed by cisplatin and vinblastine maintenance therapy for 1 year. The follow-up of these patients ranges from 24 to 66 months. Forty-nine (54%) patients achieved complete remission by chemotherapy alone and 14 (15%) were rendered free of tumor by surgery after chemotherapy, for a total complete remission rate of 69%. Three complete responders relapsed within 13 months, and two died. One additional complete responder died of a non-cancer-related cause. One of the surgical complete responders relapsed and died. Overall, 58 (64%) patients remain free of disease. The 5-year survival is 95% for complete responders, 32% for partial responders, and 72% overall. This combination regimen has significantly improved the survival of disseminated testicular cancer patients, equaling that of Stage II patients in older literature.


Following the stimulating results of Einhorn and Donohue, the Dutch Testicular Cancer Study Group in May 1976 initiated a trial of cisplatin, vinblastine, and bleomycin combination chemotherapy in patients with disseminated testicular non-seminomatous cancer. The study was closed to entry in October 1979. The early results were published in 1979. In this report we will present the 5-year follow-up data.

**Materials and Methods**

Ninety-one patients were entered into the study. Age ranged from 17 to 66 years with a median of 30 and an average of 33 years. All patients had measurable metastases except two in whom raised serum levels of the β-subunit of human chorionic gonadotrophin (β-HCG) were the single indicators. The histology of the tumors was classified according to Pugh (Table 1). The extent of the disease was assessed according to Samuels and associates (Table 2).

The patients were treated with 3 to 4 cycles of cisplatin 20 mg/m² IV daily times five and vinblastine 0.2 mg/kg IV daily times two, every 3 weeks. Bleomycin 30 mg IV was started on day 2 of the first cycle and repeated weekly times twelve. The first 17 patients received only 3 cycles of induction therapy. During cisplatin administration diuresis was maintained with 4 liters of saline per 24 hours. Cisplatin was given as a 4-hour infusion, vinblastine as an IV bolus. Bleomycin was administered as a short IV infusion of 15 to 30 minutes. When diuresis was less than 600 ml/6 hours, 100 ml mannitol 20% was given and if necessary repeated with furosemide 5 to 10 mg IV. After completion of remission induction chemotherapy, complete responders received maintenance chemotherapy with vinblastine 0.3 mg/kg alternating with cisplatin 50 mg/m² plus vinblastine 0.2 mg/kg at 3 weeks intervals. Initially the duration of maintenance therapy was 2 years; this was shortened to 1 year as of January 1978.

Complete remission was defined as a complete disappearance for at least 8 weeks of all clinical, radiographic, and biochemical evidence of disease, which included the results of whole-lung tomography, CT scanning of the abdomen, exploratory surgery and assays of β-HCG and α-fetoprotein (AFP).

Partial remission was defined as a decrease of 50% or more in the sum of products of the perpendicular di-
Table 1. Results of Chemotherapy in Relation to Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. patients</th>
<th>CR</th>
<th>PR</th>
<th>Tox D</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MTI</td>
<td>18</td>
<td>9</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MTT</td>
<td>62</td>
<td>36</td>
<td>20</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>49</td>
<td>33</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

TD: teratoma differentiated = mature teratoma; MTI: malignant teratoma intermediate = teratocarcinoma; MTT: malignant teratoma undifferentiated = embryonal cell carcinoma; MTT: malignant teratoma trophoblastic = choriocarcinoma; CR: complete remission; PR: partial remission; Tox D: toxic death.

Parameters of all measurable lesions for at least 8 weeks. In case of tumor progression the patient went off study.

Results

Forty-nine (54%) patients achieved a complete remission with chemotherapy alone. Thirty-three (36%) achieved partial remission, four patients showed progression of disease after an initial short response, and five patients died of toxicity (Table 1). Two patients died of bleomycin-induced lung fibrosis at cumulative dosages of 240 and 330 mg, respectively. Two patients died of agranulocytic sepsis, and one of myocardial infarction during hemodialysis for renal failure due to cisplatin.

The major determinant of prognosis appeared to be the extent of the disease (Table 2). Patients with a minimal tumor load had a 78% to 100% chance of complete remission, whereas patients with advanced disease had a worse prognosis with 51% to 60% complete remissions. To date, 15 patients had advanced abdominal plus advanced pulmonary disease. Of these, only two (13%) achieved complete remission, whereas all four patients who developed progressive disease during induction chemotherapy belonged to this very advanced disease category.

The results of induction chemotherapy were not significantly influenced by previous therapy (Table 3). Of 36 patients who received either previous radiotherapy or chemotherapy or the combination of both, 18 (50%) achieved complete remission as compared with 31 of 55 (56%) in nonpretreated patients. However, four of five patients who died of toxicity were in the pretreated category. Previous radiotherapy with or without chemotherapy was indeed accompanied by increased toxicity during induction chemotherapy (Table 4).

Forty-eight (53%) patients underwent exploratory surgery (Table 5). Of these, seven were marker positive as evidence of active disease, which was confirmed historically. Thirty-two had elevated serum tumor markers (β-HCG and/or AFP) at the start of chemotherapy, which had fallen to normal levels before surgery. Five patients (16%) were found to have residual viable cancer, 8 (25%) had residual mature teratoma, and 19 (59%) had normal architecture or fibronecrotic tissue only. Nine patients had normal serum tumor markers from the start of chemotherapy. Of these, none had viable cancer cells at surgical exploration, four (44%) had mature teratoma, and five (56%) had residual fibronecrotic changes or normal architecture.

Of the patients with residual tumor, 4 with cancer and 10 with mature teratoma were considered to be rendered free of tumor by the surgery (Table 6). Overall, 63 (69%) patients achieved disease-free status. Three complete responders by chemotherapy alone relapsed after 7, 12, and 13 months, respectively, and two died. One of the 14 complete responders to the combination of chemotherapy and surgery, a patient with an undifferentiated malignant teratoma, relapsed and died. Another patient died of myocardial infarction 14 months after the achievement of myocardial infarction 14 months after the achievement of myocardial infarction 14 months after the achievement.

Table 2. Results of Chemotherapy in Relation to Extent of Disease

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>No. patients</th>
<th>CR</th>
<th>PR</th>
<th>Tox D</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPD</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>APD</td>
<td>25</td>
<td>15</td>
<td>7</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>MAD + MPD</td>
<td>5</td>
<td>5</td>
<td>100%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AAD</td>
<td>35</td>
<td>18</td>
<td>51%</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>AAD + APD</td>
<td>15</td>
<td>2</td>
<td>13%</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>B-HCG only</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

MPD: minimal pulmonary disease; APD: advanced pulmonary disease; MAD: minimal abdominal disease; AAD: advanced abdominal disease; Tox D: toxic death.

Table 3. Results of Chemotherapy in Relation to Previous Treatment

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>No. of patients</th>
<th>CR</th>
<th>PR</th>
<th>Tox D</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRT and/or CHT</td>
<td>36</td>
<td>18</td>
<td>50%</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>No prior treatment</td>
<td>55</td>
<td>31</td>
<td>56%</td>
<td>21</td>
<td>1</td>
</tr>
</tbody>
</table>

XRT: radiotherapy; CHT: chemotherapy.

Table 4. Toxicity of Chemotherapy in Relation to Previous Treatment

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>No. of patients</th>
<th>Granulocytopenia*</th>
<th>Thrombocytopenia†</th>
<th>Renal failure‡</th>
<th>Sepsis§</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRT and/or CHT</td>
<td>36</td>
<td>22 (61%)</td>
<td>11 (30%)</td>
<td>13 (35%)</td>
<td>12 (33%)</td>
</tr>
<tr>
<td>No prior treatment</td>
<td>55</td>
<td>17 (31%)</td>
<td>6 (11%)</td>
<td>5 (9%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

* Less than 0.5 × 10⁹/l for 5 days or more.
† Less than 50,000 × 10⁹/l for 5 days or more.
‡ Serum creatinine above 120 μmol/l.
§ Blood culture proven.
of complete remission. Therefore, 58 (64%) patients remain disease-free after a follow-up period of 24 to 66 months.

The survival curves, calculated by the Kaplan-Meier method, are represented in Figure 1. Note that the majority of the patients have a follow-up of 2 to 4 years, and that no patient has died after 29 months of follow-up. To date, the probability of surviving 66 months is 95% for complete responders, 32% for partial responders, and 72% overall. The single complete responder who died of myocardial infarction after 16 months of follow-up is considered lost to follow-up at that point, to avoid that the survival estimates would include risk factors other than cancer death.

**Discussion**

Cisplatin-based induction chemotherapy has dramatically improved the prognosis of patients with disseminated testicular nonseminomas, resulting in long-term disease-free survival rates of 68% to 84% of patients. Our study shows that once a complete remission has been carefully documented, the 5-year survival chance is 95%. It is striking to observe that the survival results of today's treatment of Stage III are better than those of Stage II disease in the 1960s.9

The role of maintenance chemotherapy is questionable. The Southeastern Cancer Study Group8 has executed a randomized study of maintenance chemotherapy with vincristine or no further therapy. Nine of 113 (8%) patients relapsed with no differences between the arms. At Memorial Sloan-Kettering Cancer Center (MSKCC) two subsequent groups of complete responders to the VAB-6 regimen received either maintenance therapy with vincristine and dactinomycin or no further therapy. The relapse rate did not differ.10

In our study, with the use of maintenance therapy with cisplatin and vincristine, the relapse rate is 4 of 63 (6%), which suggests that this regimen also fails to reduce the chance of relapse. We no longer use maintenance therapy.

Several studies have shown that the extent of metastatic disease is the major prognostic factor.1,2,4,7,11 Also, in our patient series the chance of achieving complete remission fell sharply with increasing tumor volume (Table 2). In our view, it is essential to develop a different therapeutic approach to patients with high-volume metastases by implementing new active agents such as VP-16-213, which is the second most active drug next to cisplatin.12-16 Since Williams and Einhorn16 achieved 18 (40%) long-term complete remissions with induction chemotherapy including cisplatin and VP-16-213 in 45 patients who had failed PVB, it is obvious that these regimens are not cross-resistant. For this reason, it may be warranted to use these combinations alternatingly in first line treatment of patients with high-volume metastases.

At Indiana University17 and MSKCC18 experience has been gained with cytoreductive surgery following induction chemotherapy. In 12 of 52 (23%) and 11 of 37 (30%) patients, respectively, who were marker negative at the time of surgery, residual viable cancer was detected in the resected specimens. If one would argue that immature teratoma should be included in the category of residual malignant disease, the score at Indiana University was 16 of 52 (31%). In our patient series we have found residual viable cancer in only 5 of 41 (12%) patients who were

![Fig. 1. Survival curves calculated by the Kaplan-Meier method.](image-url)
marker negative at the time of surgery (Table 5). Twelve of 41 (29%) had mature teratoma, and 24 patients (59%) had either fibrotic changes (17 patients) or normal architecture (7 patients). We do not see an explanation for the relatively low percentage of persistent malignant disease and the conversely high rate of patients with fibrotic tissue or normal architecture in our series. According to the criteria of Samuels and associates our patient population showed initial bulky disease in 75 of 91 (82%) of the cases, and only 2 of 7 patients with normal architecture and 3 of 17 patients with fibrotic changes had minimal abdominal or pulmonary metastatic disease at the start of induction chemotherapy. Our study confirms that the prognosis of patients with mature teratoma is extremely good with no relapses in that patient group.

As we have reported earlier, previous radiotherapy and chemotherapy increase the risk of severe side effects and toxic death (Table 3). To avoid this, we consider patients with roentgenologically demonstrated retroperitoneal lymph node metastases, larger than 2 cm in diameter, candidates for primary PVB induction chemotherapy. This approach is further justified, because this patient category runs a high risk of developing progressive metastatic disease after radiotherapy or retroperitoneal lymph node dissection with or without nonaggressive adjuvant chemotherapy. The lethal toxicity in our study was limited to the first 2 years of our experience. As demonstrated by Einhorn and Williams bone marrow depression and infectious complications can be significantly reduced by decreasing the dose of vinblastine to 0.3 mg/kg per treatment cycle without loss of therapeutic activity.

The late toxic manifestations that we have observed are predominantly of neurologic nature with paraesthesia in hands and feet. These complaints are more persistent in patients who have completed their full maintenance chemotherapy. After having been off treatment for 2 years hardly any patient reported this side effect and the few who did experienced minimal paraesthesia only in circumstances of physical tiredness or when the weather changed suddenly. The phenomenon of Raynaud has been reported elsewhere in the literature, and has also been observed in our patient series. A symptom, not yet described, is Hhermite’s sign, which denotes an electric sensation radiating down the spine into the arms and legs upon flexion of the head. This symptom was observed in three patients who were off treatment. This was of short duration in two patients, but lasted for several months in one. The latter patients also had severe abnormalities on electromyogram. We have not observed late side effects to the kidneys, the cardiovascular system, or the respiratory tract.

In conclusion, the data of this study show that the 5 year survival rate of patients with disseminated testicular non-seminomas is 72% with an expected cure rate of 65%.

REFERENCES