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Perspectives and Commentaries

Have New Aggressive Chemotherapy Regimens Improved Results in Advanced Germ Cell Tumors?

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IN Vol. 22 No. 4 of the *European Journal of Cancer and Clinical Oncology*, Doctors Daugaard and Rørth from the Finsen Institute present very impressive data with a high dose chemotherapy regimen of cisplatin plus VP-16 (together with bleomycin) in poor prognosis germ cell tumor patients. Although their results are excellent, it is nevertheless appropriate to critically examine whether this or similar aggressive regimens have truly improved survival in advanced disease patients.

STAGING SYSTEMS AND PROGNOSTIC VARIABLES

The first important issue is determining which patients with germ cell tumors have advanced disease and would be candidates for more aggressive (and therefore, by definition, more toxic) chemotherapy. No author disputes the fact that advanced patients have a relatively poor prognosis with "standard dose" cisplatin plus vinblastine (or VP-16) plus bleomycin; however, not all authors agree on the criteria for advanced disease. Tumor volume, variously defined, is important prognostically in all series. Serum markers, especially HCG, is independently important in most, but not all series [1–4].

At Indiana University, we have developed a staging system that places patients with disseminated germ cell tumors into three separate categories (minimal, moderate, or advanced). This staging system is depicted in Table 1 [4]. Table 2 demonstrates the therapeutic outcome of these patients. The denominator is the total number of patients in each category and the numerator represents the number of patients who achieved a disease-free (NED) status, either with "standard" chemotherapy (PVB or $PVP_{16}B$) alone, or with surgical resection of residual tumor. It should be noted that our "moderate" category included patients who did extremely well with standard chemotherapy with 50 of 55 (91%) achieving an NED status. These patients would have been classified as advanced disease in many other staging systems and would have been inappropriately subjected to a newer more aggressive chemotherapy regimen as opposed to standard chemotherapy.

A recent British study, from six separate centers treating patients from 1976 to 1982, also identified three separate prognostic categories with respective 3 yr survivals of 91, 72, and 47%, and overall a 75% 3 yr survival [5]. Therapeutic results improved with the passage of time, presumably due to more familiarity of cisplatin combination chemotherapy regimens and surgical resection of residual disease. This dramatic improvement, based upon the year of treatment, is shown in Table 3. If the 1981–2 regimen were a newer, more aggressive regimen, the authors might have erroneously believed a therapeutic advance had been made, compared to the 1976–8 regimens. This demonstrates the hazard of historical control analysis to document superiority of a "new" regimen. The improved results with time were seen in "advanced" patients as well as less advanced cases.

A similar demonstration of the importance of the year of chemotherapy was also observed in patients with disseminated germ cell tumors treated at Indiana University (Table 4). Our original regimen (1974–6) consisted of cisplatin plus vinblastine plus bleomycin (PVB). Our second study demonstrated that we could achieve identical therapeutic results with reduction in hematological and neuromuscular toxicity by reducing the vinblastine dosage 25% from 0.4 to 0.3 mg/kg. Our

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Table 1. *Indiana University Staging System*

Minimal Extent

1. Elevated markers only
2. Cervical nodes (+/− nonpalpable retroperitoneal nodes)
3. Unresectable nonpalpable retroperitoneal disease
4. Less than 5 pulmonary metastases per lung field and largest < 2 cm (+/− nonpalpable retroperitoneal nodes)

Moderate Extent

1. Palpable abdominal mass only (no supradiaphragmatic disease)
2. Moderate pulmonary metastases: 5–10 metastases per lung field and largest < 3 cm, or solitary pulmonary metastasis of any size greater than 2 cm (+/− nonpalpable retroperitoneal disease)

Advanced Extent

1. Advanced pulmonary metastases: Primary mediastinal germ cell tumor or > 10 pulmonary metastases per lung field, or multiple pulmonary metastases with largest greater than 3 cm (+/− nonpalpable retroperitoneal disease)
2. Palpable abdominal mass plus supradiaphragmatic disease
3. Liver, bone, or CNS metastases

third generation study documented that optimal cure rates could be achieved with 12 weeks (four courses) of PVB, and that maintenance vinblastine was unnecessary. Our cure rate increased from 57 to 80% with the *identical* chemotherapy regimens, except for reduction in vinblastine dosage and elimination of maintenance vinblastine. Unfortunately, many "new improved" regimens compare their results in a small number of patients with brief follow-up to our original regimen (1974–1976), despite the fact that their new more aggressive regimens were all given in the 1980s. Such claims of superiority obviously must be viewed with caution if not skepticism.

RESULTS WITH STANDARD CHEMOTHERAPY IN ADVANCED DISEASE

Cisplatin plus VP-16 plus bleomycin ($PVP_{16}B$) has been recently utilized as initial chemotherapy, both in Europe and the United States. Peckham *et al.* treated 43 patients with 37 (86%) presently NED. Cisplatin was given in a dosage of 20 mg/M^2 × 5, bleomycin 30 mg weekly and VP-16 120 mg/M^2 days 1–3. Fourteen of these patients had advanced disease, and 12 (86%) were continuously NED at the time of the publication [6].

From 1981 to 1984, the Southeastern Cancer Study Group (SECSG), of which Indiana University is a member, randomized patients with disseminated germ cell tumors to 12 weeks of PVB vs. 12 weeks of $PVP_{16}B$ [7]. The cisplatin and bleomycin in both regimens were the same (20mg/M^2 × 5 every 3 weeks for four courses and 30 units weekly × 12). The vinblastine dosage was 0.15 mg/kg days 1–2 and VP-16 was 100 mg/M^2

Table 2. *Therapeutic results from Indiana Staging System*

Minimal	Moderate	Advanced
102/103 (99%)	50/55 (91%)	43/81 (53%)

All patients were treated at Indiana University from 1978–1983.

Table 3. *Multicentre British study*

Year(s)	No. patients	3-yr survival rate
1976–8	110	68%
1979	102	72%
1980	101	81%
1981–2	145	89%

Table 4. *Sequential PVB studies at Indiana University*

Study No.	Patients	C.R.	NED with surgery	Presently NED
1 (1974–6)	47	3 (70%)	5 (11%)	27 (57%)
2 (1976–8)	78	51 (65%)	13 (17%)	57 (73%)
3 (1978–81)	147	92 (63%)	31 (21%)	117 (80%)

Table 5. PVB vs. $PVP_{16}B$ — Southeastern Cancer Study Group

	PVB	$PVB_{16}PB$
No. patients	116	121
C.R.	73 (62%)	69 (57%)
NED with surgery	13 (12%)	25 (21%)
Total NED	86 (75%)	94 (78%)

Table 6. SECSG PVB vs. $PVP_{16}B$

	PVB	$PVP_{16}B$
No. patients	116	121
NED minimal	52/54 (96%)	54/56 (97%)
NED moderate	22/26 (85%)	23/30 (77%)
NED advanced	12/36 (33%)	17/35 (48%)

× 5 every 3 weeks for four courses. The overall results for the entire patient population is shown in Table 5. Although the therapeutic results were equivalent, $PVP_{16}B$ was the preferred regimen because of a statistically significant reduction in neuromuscular toxicity [7]. Utilizing the M.D. Anderson staging system [1], 90 of 137 advanced patients (66%) achieved an NED status with PVB or $PVP_{16}B$. The prospective results with the Indiana staging system [4] are depicted in Table 6. These results are slightly different from those in Table 2, as Table 6 represents all patients treated in a cooperative group, including Indiana University, from 1981 through 1983 and Table 2 depicts the results from a single institution (Indiana) from 1978 to 1983.

Dr. Pizzocaro and colleagues recently published their results with $PVP_{16}B$ in advanced germ cell patients [8]. Cisplatin dosage was 20 mg/M^2 × 5, VP-16 100 mg/M^2 × 3 and bleomycin 30 units weekly. Forty patients were treated from August 1981 through November 1983. Any patient with > 10 cm abdominal mass, > 5 cm pulmonary nodule, metastases outside nodes and lung (e.g., liver, bone, CNS), serum alphafetoprotein > 1000 Ng/ml or serum HCG > 50,000 mIU/ml was eligible. Thirty-seven of 40 (92%) achieved an NED status, and with a median followup of 24 months (range 13–40 months) 34 (85%) remain NED.

NEW REGIMENS FOR ADVANCED DISEASE

Newlands *et al.* at Charing Cross have reported their results with a very complicated alternating chemotherapy regimen involving seven different drugs ("POMB/ACE"). The average duration of therapy was 6 months (range 3–9).

Furthermore, all patients also received three doses of intrathecal methotrexate. Sixty-nine patients (only 2/3 had advanced disease) were treated from 1979 to 1982. Life table analysis projects 83% survival [9]. The mean follow-up was 16 months (range 2–36). Although the authors felt this represented an advance compared to standard therapy, these results were not superior to contemporary series of patients treated at Indiana University (Table 4), or by Dr. Pizzocaro [8] or Dr. Peckham [5, 6] utilizing standard dose cisplatin plus VP-16 plus bleomycin. Furthermore, the results at Charing Cross with POMB/ACE were not superior to other British centers utilizing PVB or cisplatin plus VP-16 plus bleomycin in the multicentre study evaluating prognostic variables [5]. Although these patients were not randomized, the 3 year survival with POMB/ACE was 79% compared to 82% with the more standard regimens [5].

Another author who claims superior results is Dr. Logothetis from M.D. Anderson [10]. He employed an equally complicated, extremely aggressive five-drug regimen in 48 patients ($CISCA_{II}/VB_{IV}$).

Forty-five per cent of all courses were associated with granulocytopenic fever and 25% had bacteriologically documented septicemia, and an additional two patients developed candidemia. Although 37 (77%) patients had advanced disease, presumably a significant number would not have been classified as "advanced" by the Indiana staging system [4]. Also, extragonadal presentations were not included in this series. Nevertheless, the therapeutic results were good, as 44 of 48 (92%) patients achieved an NED status.

Table 7. Eligibility criteria PVeBV vs. PVB

1. Advanced abdominal disease:
   (a) > 10cm or palpable abdominal mass;
   (b) liver metastases.
2. Advanced lung disease:
   (a) mediastinal mass or pulmonary nodule > 5 cm;
   (b) multiple nodules (> 5) with at least one > 2 cm;
   (c) > 5 metastases per lung field if each lesion is > 1.0 cm;
   (d) pleural effusion;
   (e) hypoxia ($p0_2$ < 75 mm Hg).
3. Other:
   (a) pure choriocarcinoma;
   (b) extragonadal primary;
   (c) CNS metastases;
   (d) other visceral metastases;
   (e) AFP > 1000;
   (f) HCG > 10,000.

An innovative aggressive regimen for advanced testis cancer was devised by Ozols and colleagues at the National Cancer Institute, U.S.A. This pilot regimen tested double dose cisplatin (40 mg/M^2 × 5) combined with vinblastine, VP-16, and bleomycin. Starting in May 1981, the NCI next performed a randomized study comparing the new regimen to standard PVB. As of 7/1/85, 46 patients have been entered on this 2 : 1 randomization (30 on double dose cisplatin combination regimen and 16 on standard PVB). The eligibility criteria is shown in Table 7. The cisplatin dosage was 40 mg/M^2 for 5 consecutive days, vinblastine 0.2 mg/kg on day 1, VP-16 100 mg/M^2 for 5 consecutive days and bleomycin 30 units weekly, with courses repeated every 3 weeks (PVeBV). Twenty-six of 30 patients (87%) achieved a C.R. with PVeBV, and 21–30 (70%) are continuously NED. There were two drug deaths secondary to bleomycin, one death from recurrent embryonal carcinoma (malignant teratoma undifferentiated), and two patients had recurrent teratoma (teratoma differentiated). In this randomized study, 10 of 16 (62%) achieved a C.R. on standard dose PVB; however, only 5 of 16 (31%) are continuously NED (one death due to bleomycin pulmonary fibrosis, two patients with recurrent embryonal carcinoma, and two patients with recurrent teratoma). The interim comparative analysis of PVeBV vs. PVB is shown in Table 8 as well the two-sided *P*-values for differences for each parameter (RF Ozols, pers. comm.). While there is a trend favoring PVeBV, after 4 yr the only parameter which currently has achieved statistical significance relates to the number of patients who are alive and without recurrent embryonal cancer or teratoma ($P = .027$).

The numbers of patients on this important study, even after 4 yr, is still too small to make definitive conclusions concerning the value of PVeBV vs. PVB. Furthermore, all patients in category 1(a) and some patients in categories 2(a), 2(b), 2(c), 3(a), 3(b), 3(c), and 3(f) may not have been categorized as advanced disease by the Indiana or other staging systems (Table 7).

The study of high dose cisplatin plus VP-16 reported by Drs. Daugaard and Rørth was an original and logical regimen. Cisplatin had been shown to be dose dependent in a Southwestern Oncology Group study, as 120 mg/M^2 was superior to 75 mg/M^2, when combined with vinblastine plus bleomycin [11]. Further escalation of cisplatin is logical. Likewise, very high dose VP-16 with autologous bone marrow transplantation can achieve remission in patients refractory to standard dose VP-16 [12]. Advanced disease was defined as: > 10 cm abdominal nodes, liver metastases, > 5 cm supradiaphragmatic metastases, multiple pulmonary metastases with at least one > 5 cm in diameter, extragonadal primary with elevated marker(s), or HCG > 100,000. Drug dosages were cislatin 40 mg/M^2 × 5 plus VP-16 200 mg/M^2 × 5 plus bleomycin 15 mg/M^2 weekly. Nineteen of 22 patients (86%) achieved complete remission, and 17 (77%) are presently NED after median followup of 11 months (range 1^+ to 19^+ months). However, toxicity was severe. One patient died of respiratory failure within 10 days of starting chemotherapy and another died of cardiac failure after one cycle (? drug related). Two patients in complete remission died with thrombocytopenia and granulocytopenia after 1 and $1\frac{1}{2}$ cycles and an additional patient died after 6 cycles with mycotic infection in the lung and heart. A total of 74 cycles were given to these 22 patients, and in 15 patients (73%) the WBC was < 1000

Table 8. PVeBV vs. PVB

	PVeBV	PVB	*P* value
Complete response	26/30 (87%)	10/16 (62%)	0.13
Death rate			
All causes	7/30 (23%)	8/16 (50%)	0.14
Embryonal carcinoma	5/30 (17%)	7/16 (44%)	0.087
Continuously NED	21/30 (70%)	5/16 (31%)	0.027

(median 7 days, range 1–15 days) and in 16 patients (74%), the platelet count was < 25,000 (median 6 days, range 1–18 days). Twenty of 22 patients (91%) had at least one incidence of granulocytopenic fever and 68% had two to five cases of neutropenic fever, including four cases of documented bacteremia. In addition, diarrhoea ocurred in 31% of the cycles, hypomagnesemia was seen in all patients, and two patients had a functional hearing impairment that has required the use of a hearing aid.

CONCLUSIONS

1. Staging systems for "advanced" disease vary in different series. Some regimens may well have excellent results because of inclusion of favorable patients (e.g., moderate disease patients in the Indiana staging system).
2. The major reason for chemotherapy failure and subsequent death in patients with germ cell tumors is clearly related to bulk advanced disease. However, another cause of treatment failure is moderate or bulky teratoma (teratoma differentiated) which persists post-chemotherapy, and is not surgically resectable [13]. Likewise, teratoma may be associated with non-germ cell elements which are equally chemoresistant as teratoma [14]. More aggressive chemotherapy will not solve these problems related to teratoma.
3. New regimens in the 1980s are better than the older (e.g., PVB) regimens of the 1970s. However, the older regimens in the 1980s such as PVB and $PVP_{16}B$ are also better than the same regimens when they were utilized in the 1970s (Tables 3 and 4). If historical controls are to be used, we need to match them to similar volume patients from contemporary series. Only two authors categorically claim superiority with their newer regimens [9, 10]. However, I would tend to agree with the last statement in Daugaard and Rørth's abstract: "Only a prospective randomized study can substantiate whether this excess in toxicity can be translated into an improved survival and cure."

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