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Review

Testicular cancer and the legacy of chemotherapy

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Summary. The treatment of testicular cancer has undergone considerable evolution since the introduction of cisplatin and the widespread recognition of its curative potential in all stages of disease. Chemotherapy developments that have taken place include substitution of etoposide for vinblastine in some primary combinations and high-dose cisplatin regimens for patients with otherwise poor prognosis. Definition of timed survival restaging and reassessment of the role of radiation has taken place. In early disease stages, dissection of retroperitoneal nodes combined with either a short course of adjuvant chemotherapy or careful monitoring followed by salvage chemotherapy has yielded impressive results (>90% cures) in node positive patients. These results have encouraged trials including careful follow up for patients with negative retroperitoneal and other findings (markers, computerized tomography) on clinical staging alone. Evolution of these treatment strategies should take place within the context of prospectively designed studies. In this brief overview of developments, we point out how the legacy from the successful application of chemotherapy will form the basis for additional achievements which will include the introduction of secondgeneration drugs and optimization of combined modality strategies.

Introduction

The introduction of cisplatin-containing regimens in the mid-1970s initiated an era of curative strategies for the treatment of all stages of testicular cancer [28]. Age-adjusted mortality statistics indicated a decline by one-third between 1973 and 1978, compared with stable rates during the preceding decade [26]. This decline was due to improved survival of patients with nonseminomatous cancer who had disseminated disease at initial diagnosis.

Several developments have taken place since the initial implementation of the first reproducibly successful chemotherapy regimens. These developments are an excellent example of the returns in human terms from chemotherapy efforts in both the laboratory and the clinic. We shall describe the current status of testicular cancer treatment by reviewing (1) evolution in chemotherapy; (2) concepts of surgery and radiation as an adjuvant to chemotherapy; (3) evolution of therapeutic strategies for stages I and II, and (4) delineation of prognostic factors. The stimulus for these changes has been the introduction of new drugs effective in relapsing patients (i.e., etoposide), the definition of high-risk groups requiring additional treatment strategies, and efforts to diminish the morbidity associated with standard chemotherapy regimes while recognizing that optimal use of currently available therapeutic modalities can continue to enhance their therapeutic index and bring about further improvement in overall results.

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I. Evolution in chemotherapy

The results of *standard chemotherapy* with cisplatin, vinblastine, and bleomycin (PVB) or modifications (Table 1) in advanced disease have been universally confirmed. Two U.S. Oncology Group studies (SWOG, ECOG) appear to indicate a dose-dependent response for cisplatin, so that higher doses give higher greater percent ages of complete remissions [9, 36]. The focus has been on the development of newer regimens including etoposide, the identification of high-risk groups who require more intensive chemotherapy, and the evaluation of long-term and acute morbidities [9, 12–14, 18, 35, 36, 38, 40, 41, 43, 48]. It is important to point out that such chemotherapy is also increasingly contributing to the treatment of seminoma and extragonadal tumors [2, 8, 15, 17, 20, 23, 33, 46].

Etoposide was identified as an effective agent when used in salvage regimens, mostly with cisplatin and occasionally bleomycin [21, 25]. It has been incorporated into the initial treatment of testicular cancer by Peckham and coworkers at the Royal Marsden Hospital in a regimen with bleomycin and cisplatin (BEP) [22]. This regimen is being compared with PVB by the Southeastern Group (SEG), with equivalent results to date (81% versus 73% CR) [49]. Synergy between cisplatin and etoposide, a concept suspected in the laboratory and verified in clinical studies, is probably a factor in these favorable results [7].

Having seemingly equivalent efficacy as initial treatment, etoposide regimens may have advantages in patient acceptance and in long-term morbidity. For example, the troublesome Raynaud's phenomenon may be avoided. It has been related to the added effects of vinblastine and cisplatin neuropathies, to hypomagnesemia, and to distal extremity bleomycin skin toxicities [47]. Pericarditis has also been reported with PVB [1].

Table 1. Chemotherapy of testicular cancer: Summary of series since addition of cis-platinum

Reference	Regimen	Number of patients	CR chemotherapy	CR total	Survival
[13]	$P_{20\times5}VB$	47	70%	81%	57%≥5 years
[14]	$P_{20\times5}VB \pm$ Adria	171	66%	77%	71% disease-free >1 year
[35]	$P_{15\times5}VB$	126	56%	–	–
[43]	$P_{100}VB$	58	79%	–	–
[36]	$P_{120.\ 15\times5}VB$	114	63%, 34%	62%	–
[41]	$P_{20\times5}VB$	71	58%	65%	–
[12]	$P_{varied}VB$	87	66%	78%	–
[18]	VAB CP_{120} (VAB-3)	89	62%	–	54%>3 years
[18]	VAB CP_{120} (VAB-4)	45	64%	88%	–
[48]	VAB CP_{120} (VAB-6)	25	64%	92%	–
[38]	VB/Adria $P_{20\times5}$	71	54%	–	–
[40]	VB/Adria P_{60}	102	62%	–	–
[9]	$VABCP_{80.\ 120}$	178	46%	(61%)[b]	66%>2 years
[17]	$P_{20\times5}$ VB/ consolidation	39	41%	90%	18 of 20 at 4 years

[a] Previously untreated patients only
[b] 15% achieved 'long-term partial response' (at least 1 year duration)

Abbreviations: P, cisplatin (subscript: daily dose); V, vinblastine; A, Actinomycin D; C, Cyclophosphamide; B, Bleomycin; VAB -3, -4, and -6 vary in how often the initial induction is repeated

Table 2. Chemotherapy regimens for testicular cancer

Standard PVB (every 3 weeks ×3–4)	Cisplatin	20 mg/m²/day ×5 IV
	Bleomycin	30 units IV weekly ×12
	Vinblastine	0.3 mg/kg IV
BEP (Royal Marsden) (every 3 weeks)	Cisplatin	20 mg/m² IV on days 1–5
	Etoposide	120 mg/m² IV on days 1–3
	Bleomycin	30 units IV weekly
BEP (SEG) (every 3 weeks ×4)	Cisplatin	20 mg/m² IV on days 1–5
	Etoposide	100 mg/m² IV on days 1–5
	Bleomycin	30 30 units IV weekly
PVe BV (NCI) (every 3 weeks)	Cisplatin	40 mg/m² IV on days 1–5
	Vinblastine	0.2 mg/kg IV on day 1
	Bleomycin	30 units IV weekly ×9
	Etoposide	100 mg/m² IV on days 1–5
BECIP (Mayo) (every 3 weeks)	Cisplatin	30 mg/m² IV on days 1–5
	Etoposide	130 mg/m² IV on days 1–3
	Bleomycin	15 units IV on days 1, 8, 15, 22

[a] Cisplatin given continuously in divided doses 10 mg/m² every 8 h in 1000 cm³ NS

High-risk groups are made up of those patients in whom tumor bulk at presentation is considered more than minimal (i.e.) >10-cm abdominal masses or more than 5 lung nodules >2 cm) *or* with highly abnormal marker levels [i.e., beta HCG, alpha fetoprotein (AFP) >100× and LDH >10× upper limit of normal], *or* with involvement of brain and/or liver, which are considered adverse visceral sites for metastases. The CR rates in these group are substantially lower than the 85%–95% CR achieved in patients with small-volume disseminated disease [24]. Chemotherapy to improve results in these groups has been introduced by Ozols and coworkers at the National Cancer Institute (NCI) [29] and by Richardson and coworkers at the Mayo Clinic (abstract submitted to ASCO, 1985) (Table 2). Both regimens depend on increasing the dose rate of cisplatin, one by providing the drug in hypertonic saline and the other by delivering it by continuous infusion, which may allow higher doses with a greater margin of safety. The NCI group regimen reported 15 of 17 patients achieving CR and is conducting a randomized study versus PVB [30]. The Mayo Clinic regimen produced a high number of CRs among 20 patients with the less favorable extragonadal primaries or patients failing prior therapies. It will be compared against PVB by ECOG. One of its attributes may be better patient acceptance. Other alternatives for high-risk patients are introducing autologous marrow rescue, testing alternating combinations, refining the therapeutic index of each ingredient in the combination (i.e., ble-

omycin infusions as planned by NCOG), using new active drugs (i.e., ifosfamide), and exploring combined-modality roles.

Platinum analogs represent another important development which will cause further progress in chemotherapy. Carboplatin is currently undergoing trial in germ cell tumors, and its attenuated neuro- and nephrotoxicity promises to lead to regimens with improved acceptance and hopefully equivalent efficacy. In addition, the potential for salvage regimens and exploitation of synergy with other drugs exists for both carboplatin and another analog, iproplatin.

II. Concepts of adjuvant surgery and radiation

The role of *surgery* as a salvage modality in advanced testicular cancer has come under close scrutiny. Initial 'cytoreductive' surgery was not useful in a high-risk population compared with a regimen in which chemotherapy was given first [24]. On the other hand, 'timed surgical restaging' has been a useful strategy in all trials of testicular cancer to document complete remission (and avoid continuation of toxic chemotherapy), to remove residual refractory disease (though these patients have a greater propensity to relapse), and to remove residual teratoma, which has been described with increasing frequency [17]. Normalization of markers plays a major role in the assessment of these patients and may increasingly be utilized to avoid surgery [44]. In patients with bulky seminoma, similarly, residual masses after prominent regression have almost universally disclosed necrotic fibrous tissue [27]. Therefore, it seems appropriate to forego surgical restaging in these patients if close followup (i.e., by CT scans and x-rays at no greater than 3-month intervals) is carried out.

Radiation may be an important modality in bulky retroperitoneal and mediastinal tumors, and is particularly effective against seminoma. Interest is mounting in a clinical trial for stage IIB seminoma comparing chemotherapy versus radiotherapy. For nonseminomatous tumors, the Royal Marsden group has utilized 40 Gy delivered to the retroperitoneum over 4½ weeks by a 6 MeV linear accelerator *after* chemotherapy response. Surgery was carried out 1 month after completion of radiation. Among the initial 22 patients treated in this way (PVB-radiation-surgery) 1 patient has died of disease and 1 of postoperative complications, whereas the other became disease-free. This series included 13 patients with stage IIB or more (abdominal node 2–5 cm or greater) and 9 with stages IV L1 and L2 (lung metastases <3 or multiple, none exceeding 2 cm [3].

The authors currently recommend this approach for stage IIC only [3]. It is important to emphasize that bleomycin may have enhanced pulmonary toxic effects when radiation has been used [5], and that it may also lead to intraoperative and postoperative respiratory problems (these may be avoided by use of low fractional 0_2 concentration) [19].

Table 3. Testicular cancer: Surgical concepts

1. Inguinal orchiectomy
2. Initial surgical staging (except seminoma, stage III, bulky stage II)
3. Timed surgical restaging
   - Residual tumor(s)
   - Removal of teratoma
   - Verification of CR
4. Cytoreduction

III. Therapeutic strategies in stages I and II

The impressive efficacy of chemotherapy in advanced testicular cancer is having an impact on our approaches in stages I and II. In the United States, where surgical staging by retroperitoneal node dissection has been the standard approach, a trial of careful followup in lieu of surgery for patients deemed to have clinical stage I on the basis of physical examination markers, chest and abdominal CT scans, and lymphangiograms has been instituted only at the Memorial Institute [39]. Such clinical stage I experience which demands monthly followup (physical examination, markers, x-rays of chest plus CT on alternate visits) has also been described in preliminary form by Peckham and coworkers and others [31, 32, 42]. The Intergroup Study Group sponsored by the NCI (USA) may look at a comparison in clinical stage I between observation and retroperitoneal node dissection [10], both groups receiving PVB upon documentation of recurrence.

In stage II disease verified pathologically, the role of immediate chemotherapy versus the monthly followup advocated by Einhorn, Williams and coworkers has been studied by an Intergroup protocol which has just completed accrual (May 1979 to October 1984). Definitive results of the study, with 210 patients randomized to either of these treatment policies, awaits further followup. Noteworthy are the striking efficacy of two cycles of chemotherapy in preventing relapses, and the relationship of some of the rare fatalities (four stage II patients, and four stage I patients) to noncompliance. Prognostic factors (see below) and patterns of recurrence are other important aspects of this study [10]. The chemotherapy utilized was both VAB [48] and PVB, and the two had comparable toxic effects, with VAB having more skin toxicities.

Several additional data were presented in Tucson, Arizona at the March 1984 Fourth International Adjuvant Therapy of Cancer Meeting [16]. It is of interest that pooling of all the results of patients who have had monthly followup and then been treated at the first sign of relapse reveals that there have been 8 deaths among 127 patients. This represents a 7% failure of 'salvage' treatment, which compares unfavorably with the 0/89 patients in various trials who have had retroperitoneal node dissection and immediate adjuvant chemotherapy.

IV. Prognostic factors and other issues

The Intergroup study and clinical stage I experience have also yielded important information on prognostic factors relating to recurrence in early stages of testicular cancer.

Single factors recognized in the Intergroup Study [10] as important determinants of recurrence are (1) vascular invasion ($P<0.001$); (2) embryonal elements ($P<0.02$); (3) positive lymphangiogram and/or CT scan ($P<0.02$); and (4) T2 tumor, i.e., extension along spermatic cord ($P<0.04$).

At the Arizona meeting [16], Vugrin summarized data from clinical stage I studies which included 32 of 165 patients showing recurrences (19%). Recurrences correlated

with embryonal histology and occurred in the retroperitoneum in 17 patients, in the lung in 9, and both in 3; it was recognized by means of markers in 3 patients.

In more disseminated cases, the prognostic factors in relation to 5-year survival have been analyzed by Scheulen et al. [37]. All significant parameters, such as pulmonary tumor volume, number of lung metastases, extent of retroperitoneal disease, and marker levels were ultimately most dependent on serum LDH. With LDH ≤ 240 units/l, 240 $- \leq 500$ units/l, or > 500 units/l the 5-year survival was 71%, 42%, or 14%, respectively.

Long-term consequences such as second neoplasms and irreversible fertility are among other current issues of chemotherapy of testicular cancer. It is apparent that PVB chemotherapy allows for substantial recovery in fertility [11, 45]. The Memorial group has reported on second neoplasms from 1945 to 1977, and these included contralateral primary testicular tumors in 20, leukemias in 5, and carcinoma or sarcoma in 27. The total number of 52 out of 1150 amounts to 4.5%, and does raise some concerns with the use of alkylating agents [6]. However, it is too early to exonerate cisplatin from similar problems.

The proper use of markers requires knowledge of possible errors in determination or interpretation. Cross-reactivity between LH and beta HCG is low, but does occur to a variable degree. Therefore gonadal dysfunction due to prior cryptorchidism, orchiectomy, Kleinfelter's syndrome, or cytotoxic therapy may lead to LH elevations and false-positive beta HCG. Other malignancies may cause elevation of the marker, and the use of marijuana has also been associated with transient rises. The AFP is elevated in hepatic regeneration and in genetic disorders such as ataxia telangiectasia. The possibility of distinguishing neoplastic from non-neoplastic AFP by immunologic means is being studied. Finally, the occurrence of testicular cancer in Down's syndrome and other conditions associated with gonadal dysfunction must be recognized and may shed some light on its etiology [4].

Since the initial curative studies [1] a great deal of progress has been made. The survival trends already noted in the 1982 publication [2] will undoubtedly continue to improve further, and with lesser morbidity; thus achieving a favorable balance in the triangle of host, tumor, and drug [34]. The young men that are now being cured of their previously fatal malignancies constitue a living legacy of modern chemotherapy.

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