16 Genitourinary tumors

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INTRODUCTION

The results of chemotherapy in genitourinary tumors have greatly improved during the past few years. A major advance has been achieved in particular in the treatment of testicular carcinoma since the introduction of cisplatin (see Chapter 6) in combination chemotherapy. Testicular carcinoma ranks first in the incidence of cancer in the 25-34 year age group. The relative frequencies of these tumors are: 33–50% for seminomas, 10% for pure teratomas, 10–33% for teratocarcinomas, 20–33% for embryonal cell carcinomas, and 2% for choriocarcinomas. Except for choriocarcinoma, which metastasizes early via the blood stream, the teratomas spread primarily to the retroperitoneal lymph nodes. Approximately 80% of patients with non-seminomas are found to have tumor markers: beta-subunit of human chorionic gonadotropin (β-HCG) and/or alpha-fetoprotein (AFP). In radioimmunoassays, these are very sensitive tumor markers, which do not give false positive results [1–3].

The prognosis of testicular germ cell tumors depends on the histological picture and the stage of the disease. Seminoma has the best prognosis and choriocarcinoma the worst. Until recently the prognosis for advanced non-seminomas was very poor. Since the introduction of the combination of vincristine, bleomycin and cisplatin the complete response rate and probably the cure rate for patients with advanced disease has increased to more than 50% [4, 5].

Bladder cancer comprises about 3% of all human cancers. Environmental factors influencing the distribution of bladder cancer include cigarette smoking and exposure to aniline dyes and rubber. Other forms of chronic irritation such as schistosomiasis of the bladder and chronic bacterial infection in the presence of bladder stones are predisposing factors [6–8]. Bladder tumors are of epithelial origin in 97% of the cases and tend to be of multifocal origin [6–9]. There are three histological types: transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma. The majority is formed by transitional cell carcinoma; adenocarcinoma constitutes a minority. The 1977–1978 literature has made it evident that chemotherapy of bladder
cancer has been a neglected area, but that this tumor is sensitive to chemotherapy.

Adenocarcinoma of the prostate is the second most frequent malignant tumor in the male after lung cancer, with an annual incidence of approximately 120 per 100,000 men [10]. At the time of diagnosis, only 5–10% of the patients are potentially curable by radical prostatectomy. Other treatment modalities are thus of prime importance in the management of this disease. Chemotherapy has been poorly evaluated in cancer of the prostate, primarily due to difficulties in staging and the uncertainty about the value of indicator lesions.

Renal cell carcinoma occurs most often after the age of 50 years. There is a male preponderance in the ratio of 2 to 1. At the time of diagnosis, about half of the patients have advanced metastatic disease. Spontaneous regression occurs in only 0.3% of all cases, mostly in males [11–13]. In 95% of the cases the site of regression is in the lung. The 5- and 10-year overall survival rates for metastatic renal cell cancer are 5% and 0%, respectively [14]. This tumor is very resistant to chemotherapy. No major advances leading to improvement were made in 1977–1978.

Penis carcinoma is a squamous cell carcinoma, resembling other squamous cell carcinomas of the skin. The tumor is rare, representing 1–3% of cancers in the male in the United States. There are some indications in the 1977–1978 literature that bleomycin and cisplatin will prove to be valuable drugs for the treatment of advanced carcinoma of the penis.

**TESTICULAR CANCER**

**Clinical and pathological staging**

Several staging systems are in use for non-seminomas. Despite the divergent nomenclature used for the different staging systems, the systems are basically similar. The recent systems identify patients with (1) testicular disease only, (2) minimal retroperitoneal disease, (3) gross retroperitoneal disease, and (4) organ involvement or supradiaphragmatic disease. Samuels developed the following staging system for patients with advanced disease: (A) minimal pulmonary disease, (B) advanced pulmonary disease, (C) minimal abdominal plus pulmonary disease, (D) advanced abdominal disease, and (E) elevated serum B-HCG with no other evidence of disease [15]. This system appears to correspond well with the results of chemotherapy, A being the most and D the least sensitive. Additional to the uniform procedures, clinical staging for testicular tumors requires the following special procedures: tomography of the lungs, lymphography, urography, venacavography if indicated, and assays of β-HCG and AFP [16, 17]. There appears to be a good correlation between computerized tomography and tumor markers [18, 19]. A recent report reminds us that serum calcium levels may be elevated incidentally in patients with testicular neoplasm, as a sign of pseudohyperparathyroidism [20].

Pathological staging can only be achieved by retroperitoneal lymph node
dissection and accurate histological examination of all extirpated nodes. Most staging systems require lymph node dissection. Although pathological staging is important for the prognosis and treatment, there is a 95–99% risk of development of a neurogenic ejaculatory impotence after bilateral lymphadenectomy [21, 22].

The clinical staging of seminomas is similar to that of non-seminomas. Seminomas tend to spread early via the lymphatic system. Hematogenous metastases occur in a late stage of the disease and are only seen in a minority of the cases. Pathological staging through lymph node dissection is not indicated, because the treatment of choice is always radiotherapy to the retroperitoneal lymph nodes, which offers a cure rate amounting to 90–95% of all cases.

Chemotherapy in non-seminomas

Single-agent activity for advanced disease (Stage III)

It is widely accepted that Stage III testicular non-seminomas should be treated primarily with chemotherapy. Recently Anderson et al. [23] reviewed the therapy of testicular non-seminomas comprehensively. Almost all anti-neoplastic agents show some level of activity in these tumors (Table 1). The most active drugs are vinblastine, bleomycin, and cisplatin. Although mithramycin has given promising results in the past, the response rate is probably lower than indicated in Table 1. Actinomycin-D has certainly shown activity, but bone marrow toxicity means some degree of restriction with respect to combination regimens. Alkylation agents have shown activity, although the number of patients in whom each of them has been studied is quite small. Adriamycin is not a very active drug as a single agent for the treatment of testicular tumors. The duration of the response obtained with single-agent treatment rarely exceeds one year.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>No. of responders</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>Phenylalanine mustard</td>
<td>42*</td>
<td>19</td>
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<tr>
<td>Cyclophosphamide</td>
<td>14</td>
<td>4</td>
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<tr>
<td>Ifosfamide</td>
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<td>Chlorambucil</td>
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<td>2</td>
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<tr>
<td>Actinomycin-D</td>
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<td>9</td>
</tr>
<tr>
<td>Mithramycin</td>
<td>133</td>
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<tr>
<td>Bleomycin</td>
<td>54</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>29</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>41</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>118**</td>
<td>22</td>
<td>43</td>
</tr>
</tbody>
</table>

* Seminomas only; all other drug results from series with non-seminomas.

** Data from Chapter 6, Table 1, included.
Combination chemotherapy for advanced disease (Stage III)

After the establishment of the most active single agents, many combinations have been studied, which initially included an alkylating agent, methotrexate, and actinomycin-D [23—26]. The average complete remission rate with these combinations did not exceed 20% and cures have been obtained very rarely.

A major step forward was made by Samuels [27], who introduced the combination of high-dose vinblastine plus bleomycin. He achieved a complete response rate of 50%. Others have achieved complete response rates of 44% with a similar combination (Table 2) [28]. The most active combination appeared to be the one in which bleomycin was administered in a continuous infusion over 5 days. All three studies were non-randomized. Addition of a

Table 2. Activity of regimens based on vinblastine-bleomycin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>No. of responders</th>
<th>Response rate (%)</th>
<th>Ref.</th>
</tr>
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<tr>
<td></td>
<td>CR</td>
<td>PR</td>
<td>Overall</td>
<td>CR</td>
</tr>
<tr>
<td>VBL + BLM</td>
<td>23**</td>
<td>9</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>VBL + BLM</td>
<td>48</td>
<td>21</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>VBL + BLM</td>
<td>57*</td>
<td>28</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>VBL + BLM + ACD (VAB 1)</td>
<td>68</td>
<td>15</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>VCR + BLM + ADM</td>
<td>25</td>
<td>8</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>VCR + BLM + ACD</td>
<td>20</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

VBL = vinblastine; BLM = bleomycin; ACD = actinomycin-D; ADM = adriamycin.

* This series of patients includes the 23 patients marked**.

Table 3. Cisplatin in combination chemotherapy for testicular non-seminoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>No. of CR</th>
<th>Response rate (%)</th>
<th>Ref.</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>CR</td>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>DDP-ADM</td>
<td>27</td>
<td>5</td>
<td>19</td>
<td>70</td>
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<tr>
<td>DDP-BLM</td>
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<td>79</td>
</tr>
<tr>
<td>DDP-VBL-BLM</td>
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<td>33</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>53</td>
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<td>40</td>
<td>24</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>DDP-VBL-BLM-MTH</td>
<td>11</td>
<td>2</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>DDP-VBL-BLM-ADM</td>
<td>26</td>
<td>19</td>
<td>73</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>35</td>
<td>56</td>
<td>84</td>
</tr>
<tr>
<td>DDP-VBL-BLM-ADM-CTX</td>
<td>19</td>
<td>15*</td>
<td>79*</td>
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<tr>
<td>DDP-VBL-BLM-ACD</td>
<td>50</td>
<td>25</td>
<td>59</td>
<td>84</td>
</tr>
<tr>
<td>DDP-VBL-BLM-ACD-CTX</td>
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<td>84**</td>
<td>60**</td>
<td>86**</td>
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<td>83</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>11*</td>
<td>44*</td>
<td>88*</td>
</tr>
<tr>
<td>DDP-VBL-BLM-ACD-CTX-Pred</td>
<td>66</td>
<td>54*</td>
<td>82*</td>
<td>100*</td>
</tr>
</tbody>
</table>

ACD = actinomycin-D; ADM = adriamycin; BLM = bleomycin; CTX = cyclophosphamide; DDP = cisplatin; MTH = mithramycin; VCR = vincristine; VBL = vinblastine; Pred = prednisone.

* Combined results obtained with chemotherapy and cytoreductive surgery.

** Combined results for the VAB III and the VAB IV regimens (see text).
myelosuppressive agent such as actinomycin-D to this combination requires reduction of the vinblastine dose or its replacement by vincristine. In a small randomized study the vinblastine-bleomycin combination appeared to be superior to a combination of vincristine, bleomycin, and actinomycin-D. Besides the higher complete remission rate obtained, the median survival of patients on the regimen including vinblastine was also longer (63 weeks vs 31 weeks) [28].

These results underline the value of vinblastine in combination regimens for testicular non-seminomas.

The addition of Adriamycin to vincristine and bleomycin did not lead to improvement of the results [29].

The encouraging results obtained with cisplatin in Phase I and II studies (see Chapter 6, Table 1) led to its use in combination with other active drugs. Table 3 shows the activity of the most important regimens including cisplatin. Einhorn and Donohue have updated their results, obtained in 47 evaluable patients with a 3-drug regimen of cisplatin, vinblastine, and bleomycin after a follow-up of 26–49 months [4, 30]. This treatment yielded complete response in 33 patients (70%), in 5 of whom relapse occurred within 9 months and in one at 17 months. In addition, 5 patients who achieved partial remission with chemotherapy were rendered disease-free after the surgical removal of residual tumor tissue. At operation, 3 patients, initially diagnosed as having embryonal carcinoma, were found to have benign teratoma. Overall, 29 (62%) of the 47 patients were alive with no evidence of disease after a minimal follow-up of 26 months. Cisplatin was given in a short-term infusion, lasting 15 minutes, at a dose of 20 mg/m², for 5 consecutive days. Three to 4 cycles were given, the successive cycles starting on Day 22 of the start of the previous cycle. Adequate pre- and posthydration was given to prevent the development of renal toxicity. Vinblastine was given as an intravenous bolus of 0.2 mg/kg on Days 1 and 2 of each treatment cycle. Bleomycin (30 U) was given on Day 2 of each cycle, and also at weekly intervals between the cycles until a cumulative dose of 360 U had been reached. Other investigators achieved complete responses in 33–64% of the patients, using the same combination (Table 3). The differences in the response rates may be explained by prior chemotherapy in some studies, differences in the stage of disease, doses, schedules and modes of administration (see Chapter 6, p. 115).

In a subsequent trial Einhorn [30] reduced the vinblastine dosage by 25%, which decreased the hematologic toxicity, without apparent reduction of the therapeutic efficacy.

Other cisplatin induction regimens, including actinomycin-D, Adriamycin, vincristine or prednisolone did not result in an increase of the complete remission rate. At the Memorial Sloan Kettering Cancer Center, induction regimens have been developed with the addition of cisplatin (VAB II) and cyclophosphamide (VAB III and IV) to a 3-drug regimen of vinblastine, actinomycin-D, and bleomycin [39–42]. In addition, Adriamycin and Chlorambucil were introduced into the maintenance phase of the VAB III and IV programs, the latter differing essentially as to the dose schedule of the maintenance treatment. Similar results were reported for the VAB II, III and IV

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programs with respect to complete and overall response rates. In patients achieving a complete remission on the VAB II program, the median duration of response was 13 months. For rather short follow-up periods, the relapse rate among complete responders was lower for the VAB III (15/54) and particularly the VAB IV treatment (4/30). In most complete responders, more than 18 months had elapsed since the induction of the complete response by the combination of cisplatin, vinblastine, bleomycin, actinomycin-D and cyclophosphamide [43, 44]. Because most recurrences occur in the first year of remission induction treatment, it was estimated that a cure rate of approximately 50% could be expected with these regimens.

Toxicity associated with the induction regimens has been considerable, the most important side effects being agranulocytic sepsis, renal failure, and bleomycin-induced lung fibrosis [4, 5, 30]. However, careful planning and monitoring of the patient can prevent most of the severe toxicities. In patients previously given radiotherapy and/or chemotherapy, a reduction in the dose of vinblastine to 50–75% of the dose used by Einhorn (0.2 mg/kg on Days 1 and 2) is advised. Similar dose reductions should be applied when combinations with other myelosuppressive agents are used. Since the renal tubules are made vulnerable by cisplatin, the use of the nephrotoxic antibiotics such as gentamicin and cephalothin should be avoided [47]. One patient who developed anuria on such a combination of drugs was hemodialyzed. Renal function recovered after 2 weeks, when the creatinine clearance was 80 ml/min [5].

Maintenance chemotherapy in advanced non-seminoma

The favorable results of induction chemotherapy including cisplatin, and the long-term remissions, suggest a high cure rate. In the past, Einhorn has been using vinblastine (0.3 mg/kg every 3 weeks) for 2 years, initially with BCG immunotherapy [4]. In his most recent series, he has omitted BCG from his protocol. Others gave cisplatin alone, or in combinations as maintenance chemotherapy for as long as 2 years [48]. Since recurrences are rare after one year of complete remission, achieved with a cisplatin combination, a major question to be settled is whether any maintenance treatment is required after the achievement of a complete remission. The EORTC Urological Group is presently trying to answer this question by randomizing patients, in whom complete remission has been carefully documented, comparing no maintenance treatment versus one year of maintenance chemotherapy consisting of cisplatin and vinblastine.

Multimodality treatment in advanced non-seminomas

The best approach seems at present to perform debulking surgery 1–2 months after the initiation of chemotherapy, while selecting for this procedure only those patients in whom tumor response seems rather slow [49, 50]. Merrin [51] applied reductive surgery prior to chemotherapy in the past,
but has changed his approach and suggests reductive surgery after about 8 weeks of intensive chemotherapy if the tumor is still present at that time. With this approach, 22 out of 34 patients (65%) in a very advanced stage of the disease were still in complete remission after 13 months of treatment. Unfortunately, this approach has not been studied on a controlled basis. The aggressive approach of simultaneous excision of abdominal and thoracic tumors needs further evaluation in a randomized study. The NCI Group has been studying the value of debulking operations prior to intensive chemotherapy. The results of this study have to be awaited. The UCLA Group is presently planning a study to investigate the exact timing of reductive surgery in relation to chemotherapy.

An important problem in the evaluation of the efficacy of surgery and radiotherapy for patients with testicular tumors has been the lack of prospective randomized clinical trials.

There seems to be no major role for radiotherapy in the initial management of patients with Stage III disease in view of the effectiveness of the other modalities and the risk of complications caused by chemotherapy after radiotherapy. Radiotherapy should still be considered for patients in whom the tumor has become resistant to chemotherapy and in whom surgery has failed to remove the remaining tumor tissue.

**Multimodality treatment in Stages I and II**

Treatment of these stages of testicular non-seminomas remains controversial. There is a tendency for one therapeutic modality to predominate, while insufficient consideration is given to a combined approach. Indiscriminate use of radiotherapy has made it difficult to evaluate properly the contribution of lymphadenectomy to survival. Tyrrel and Peckham [52] have shown that there is a significant chance of local recurrence of lymph node metastases after radiotherapy in patients with a positive lymphogram and lymph nodes larger than 2 cm in diameter. Ten out of 15 patients (66%) with positive nodes larger than 2 cm in diameter showed local recurrence of the tumor, as compared with only 2 out of 14 patients (14%) with nodes measuring 2 cm or less in diameter. However, accurate staging remains difficult unless lymphadenectomy is performed. Having taken the high complication rate of chemotherapy after previous radiotherapy into consideration as well, many investigators presently give preference to histological staging based on lymph node dissection in patients with Stage I–II disease. After dissection intensive chemotherapy is indicated in the patients with advanced Stage II disease [23]. In patients with limited Stage II disease, a good approach seems to be to study tumor markers thoroughly after lymphadenectomy and start chemotherapy as soon as a rise in the level of these markers is observed. Radiotherapy cures 60–80% of patients with limited Stage II disease. Until controlled randomized studies are performed, it will be difficult to determine which of the modalities is the most adequate treatment for these patients.
Seminomas

Seminoma is one of the most radiosensitive of the solid tumors. Orchiectomy combined with radiotherapy to the retroperitoneal lymph nodes cures 90–95% of the patients, who have no detectable metastases. When the tumor is in a more advanced stage, the prognosis is poor and more aggressive therapy is needed [53]. The 3-year survival for Stage II is 70% and for Stage III 30–60%. Since most patients with seminoma are cured by radiotherapy, there are few data on chemotherapy of pure seminoma. Most of the reports on seminoma concern a few cases treated with single agents or various combination regimens. When there is proved radiation resistance, or persistence of a mass after radiotherapy, surgical excision of the remaining mass followed by chemotherapy has been advised. DeKernion [54] successfully applied a combination consisting of vincristine 1 mg/m²/week for 2 weeks, actinomycin-D 0.01 mg/kg/day for 5 days, and cyclophosphamide 300 mg/m² for 4 days to reduce an initially inoperable mass. Merrin [53] advised this treatment of both Stage II and Stage III with adjuvant chemotherapy after radiotherapy. Alkylating agents are most commonly used. Several schedules have been applied. A good one seems to be cyclophosphamide 30–50 mg/kg i.v. every 3–8 weeks. Other drugs are presently being tested in several centers. Cisplatin has shown activity [30], particularly when used in combination with bleomycin, vinblastine, and/or an alkylating agent.

Testicular tumors in children

Testicular tumors are rare in children younger than 16 years. Few reports on this topic appeared in 1977–1978 [55, 56]. Hopkins et al. published interesting results on the importance of chemotherapy after surgery in 20 patients with embryonal carcinoma. The age at diagnosis ranged from 6 months to 9 years, with a mean of 18 months. Of 9 patients who underwent only orchiectomy, 5 have died, whereas all 11 patients who received combined therapies have survived. In most of these cases chemotherapy consisted of actinomycin-D. The authors recommend retroperitoneal lymph node dissection and adjuvant chemotherapy for childhood testicular tumors in general. Although a beneficial effect of chemotherapy is suggestive, the paper [55] concerns a heterogeneous group of patients. Three patients who died had presented with metastases before 1957. In 11 patients retroperitoneal node dissection had been performed; in 9 this was not the case. Treatment results in the patients with teratocarcinoma and choriocarcinoma were poor, whereas the results in the 6 patients with teratoma were favorable. In addition to this paper, the Manchester Children’s Hospital Group [56] reviewed 3 cases of embryonal carcinoma of the testis (patients aged 1, 2 and 5 years). All 3 patients were treated with vincristine, actinomycin-D, and cyclophosphamide. Two patients died despite chemotherapy. It is quite clear that it will be difficult to perform a randomized study in such a rare childhood tumor. The best approach is probably that applied in adults.
BLADDER CARCINOMA

Clinical and pathological staging

All the main staging classifications in use at present deal essentially with the most important prognostic feature of bladder cancer, i.e. the depth of penetration or infiltration into and beyond the bladder wall [6, 8]. The TNM classification of the UICC [57] is comparable to the American classifications [8]. The UICC histopathological grading system consists of a high (G1), medium (G2) and low (G3) degree of differentiation.

Intravesical chemoprophylaxis

Bladder tumors often have a multifocal origin. At the time of resection of one tumor, there is often microscopic tumor growth at other sites in the bladder mucosa. In an attempt to reduce the recurrence rate, the topical use of cytotoxic drugs has been investigated.

Instillation of thiotepa in the bladder has been studied primarily as prophylaxis of bladder tumor recurrences [7–9, 58–61]. A randomized study was conducted by the Veterans Administration Cooperative Group [61], comparing oral administration of a placebo (48 patients), oral pyridoxine (32 patients), and intravesical instillation of thiotepa (38 patients). Treatments were compared for an average period of 31 months. It was shown that the intravesical thiotepa did not significantly decrease the number of patients who developed recurrent bladder tumors, but it did decrease significantly the frequency of recurrences per patient.

In a randomized study at the Harvard Medical School and the Massachusetts General Hospital, the prophylactic intravesical administration of thiotepa (26 patients), did not reduce the number of patients with recurrent disease either [60]. However, the frequency of recurrences per patient was not reported.

In a Polish study [9], 20 patients, who served as their own controls, had 94 recurrences during the year preceding chemoprophylaxis with thiotepa as compared with 32 recurrences during the first year of this treatment. The reported results indicate that thiotepa is of value in preventing the development of recurrences of superficial bladder tumors.

Intravesical chemotherapy

Intravesical instillation of cytotoxic drugs for the treatment of bladder cancer is under investigation [48, 62–67]. No randomized studies have been reported. The available data usually concern small series and poorly defined criteria of response. Furthermore, the results of these studies are not comparable because of different tumor stage and histopathological grade, varying previous treatment, and different drug dosage and administration interval.

Thiotepa [60, 62], adriamycin [62, 66], epodyl [65, 67] and cisplatin [48, 70] have all been reported to be effective with response rates ranging from 50–80% for each drug. The remission duration cannot be determined from
most of these reports, but seems to be short. The combination of mitomycin C and various dosages of cytosine arabinoside resulted in a response rate of 20–80%, with the best response rate for the 300 mg dosage of cytosine arabinoside [64].

At present, intravesical chemotherapy as a primary treatment should be considered experimental.

**Single-drug chemotherapy in advanced disease**

In 1978, the literature on chemotherapy of bladder cancer was reviewed by Carter [6] and DeKernion [68].

In the 1977–1978 literature several adequately performed studies have been reported on the 3 most effective agents, *i.e.* cisplatin [49, 69, 70, 73], methotrexate [71], and adriamycin [72] (Table 4).

Cisplatin (50-75 mg/m², every 3–4 weeks) has been administered to 28 patients at the Memorial Sloan Kettering Cancer Center [69]. Ten patients (36%) achieved a remission with a median duration of 5 months. The Southwest Oncology Group [70] treated 9 patients with a dose of 75 mg/m², every 3 weeks. Three patients (33.3%) achieved a remission with a median duration of 3 months. At the Roswell Park Memorial Institute [49] 19/51 patients (37.2%) achieved a remission. These patients were treated with 1 mg/kg of cisplatin weekly during the first 6 weeks and every 3 weeks thereafter. The average duration of response was 5 months. Considering the drugs investigated, cisplatin is at present the most effective cytotoxic agent in advanced bladder cancer.

Methotrexate has not been widely used in the treatment of bladder cancer. DeKernion [68] reports a remission rate ranging from 17–36%. At the Royal Marsden Hospital, varying regimes of methotrexate have been used between 1970 and 1977 [71]. Methotrexate was administered every 2 weeks in dosages of 50 mg i.v., 100 mg i.v., and 200 mg i.m., respectively. In the first treatment group, partial remissions were observed in 3 of 23 patients (13%). 12/22 patients (56%) receiving the 100 mg regime showed complete or partial regression of the lung, bone and skin metastases, with a remission duration of 6–7 months for complete responders. Eight of the 16 patients (50%) on the 200 mg regime achieved remissions, lasting for 20 months in the single complete responder. Methotrexate appears to be the second most active drug in advanced bladder cancer.

Adriamycin has been the drug most widely studied in advanced bladder cancer. In reviewing the literature, Carter [6] reported a response rate of 23%

**Table 4. Single-agent chemotherapy in advanced bladder cancer**

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of patients</th>
<th>No. of responders</th>
<th>Resp. rate (%)</th>
<th>Ref.</th>
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<td>32</td>
<td>36</td>
<td>48, 69, 70</td>
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<tr>
<td>Methotrexate</td>
<td>71</td>
<td>23</td>
<td>32</td>
<td>71</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>37</td>
<td>6</td>
<td>16</td>
<td>72</td>
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</table>

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in 235 patients (range 0–37%). The more promising results, obtained in earlier studies, led to extensive use of this drug in the treatment of bladder cancer. However, more recent reports have been less optimistic [68]. The EORTC Urological Group observed remissions in 3/18 (16%) patients treated with adriamycin [58]. At the Memorial Sloan Kettering Cancer Center, 6 complete or partial remissions (16%) have been obtained in 37 patients, with a median duration of response of 3 months. This low remission rate may have been influenced by a low performance status, extensive prior radiotherapy, and lower drug dosages [72]. Adriamycin is the third most active single agent in advanced bladder cancer.

Several drugs, including 5-fluorouracil [6, 8, 68], cyclophosphamide [68], mitomycin-C [6, 68], vincristine [68] and VM-26 [68] have been inadequately studied, not allowing any conclusions as to the role of these agents in advanced bladder cancer.

**Bilharzial bladder cancer**

Bilharzial bladder cancer is predominantly of the squamous cell type, and is quite resistant to chemotherapy. Several reports have been published by Egyptian investigators [74–77].

VM-26 in a dosage of 100 mg/m²/week i.v. gave only 1 partial remission in 24 patients with bilharzial bladder cancer [74, 75]. These workers also evaluated bleomycin, methotrexate and hexamethylmelamine as single-drug therapies in bilharzial bladder cancer. Only hexamethylmelamine appeared effective with a remission rate in 10/26 (39%) patients [74–76]. In a Phase II trial with cisplatin 20–60 mg/m², a poor response was observed with only one complete and 4 partial remissions of brief duration in 38 patients [77].

**Combination chemotherapy in advanced disease**

A number of cytotoxic drugs have been investigated in a limited number of patients (Table 5). With the combination of adriamycin (50 mg/m² i.v.) and 5-fluorouracil (500 mg/m² i.v.), given once every 3 weeks, the Yorkshire Urological Cancer Research Group obtained 7/20 (35%) partial remissions.

**Table 5. Combination chemotherapy in advanced bladder cancer**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Combinations</th>
<th>No. of patients</th>
<th>Remissions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Yorkshire Urological Cancer Research Group</td>
<td>ADM + 5-FU</td>
<td>20</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>M.D. Anderson Hospital</td>
<td>ADM + VM-26</td>
<td>27</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>MSKCC</td>
<td>ADM + CTX</td>
<td>18</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Indiana University</td>
<td>ADM + 5-FU + DDP</td>
<td>17</td>
<td>11</td>
<td>65</td>
</tr>
<tr>
<td>MSKCC</td>
<td>CTX + DDP</td>
<td>35</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>MSKCC</td>
<td>ADM + DDP</td>
<td>26</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>MSKCC</td>
<td>ADM + DDP + CTX</td>
<td>6</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>M.D. Anderson Hospital</td>
<td>ADM + DDP + CTX</td>
<td>10</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>Troner et al.</td>
<td>ADM + DDP + CTX</td>
<td>9</td>
<td>4</td>
<td>45</td>
</tr>
</tbody>
</table>

ADM = adriamycin; CTX = cyclophosphamide; 5-FU = 5-fluorouracil; DDP = cisplatin.
In 2 of the 3 complete responders, the disease-free period lasted 13 and 16 months [6].

The M.D. Anderson Hospital Group evaluated the combination of adriamycin and VM-26 in 27 patients. These investigators observed partial remissions (19%). The mean survival of the responders was 17–18 months as opposed to 6.3 months for the non-responders. The combination of VM-26 and adriamycin does not give better results than either drug as a single agent [78].

At the Memorial Sloan Kettering Cancer Center, disappointing results have been obtained with the combination of adriamycin (45–60 mg/m²) and cyclophosphamide (450–600 mg/m²). Only 3/18 patients achieved a partial remission (mean duration 5 months), indicating that adriamycin plus cyclophosphamide may not be better than either of the drugs given as a single agent [79].

At the Indiana Medical Center, cisplatin (100 mg/m²) was added to adriamycin (50 mg/m²) and 5-fluorouracil (500 mg/m²). 11/17 patients (65%) achieved a partial remission (median duration 25 weeks). The median survival of responding patients was 40 weeks as compared with 17 weeks in the non-responders [80]. This indicates that this 3-drug combination regimen is hardly better than single-agent treatment with cisplatin.

Phase II studies, conducted at the Memorial Sloan Kettering Cancer Center, using a combination of cisplatin with cyclophosphamide or with adriamycin or with both, yielded remissions in 15/35 (43%), 14/26 (54%) and 3/6 (50%) patients respectively (Table 5) [69, 81]. The combination of cisplatin and cyclophosphamide did not improve the number of remissions or the survival as compared with the results of cisplatin used as a single drug. With the combination of cisplatin, cyclophosphamide and adriamycin, remissions were observed in 9/10 patients at the M.D. Anderson Hospital [82]. In regard of the extent of the disease and the pretreatment, this patient group was comparable to that of the Memorial Sloan Kettering Cancer Center. However, a higher dose of cisplatin and cyclophosphamide was used at the M.D. Anderson Hospital.

Troner et al. [83] used the combination of cisplatin (40 mg/m²) and cyclophosphamide (500 mg/m²) and adriamycin (50 mg/m²), at 3-week intervals. He achieved 4/9 (45%) remissions, one of them complete.

The results of these studies indicate that none of the investigated combinations including cisplatin has given better results than cisplatin as a single agent.

Adjuvant chemotherapy

At the Roswell Park Memorial Institute, 25 patients were given cyclophosphamide plus adriamycin as adjuvant chemotherapy, after radical cystectomy. Two patients with Stage I disease have been free of disease for 12 and 15 months, and 3 patients with Stage II disease for 25 months. 2/3 patients with Stage III disease have been free of disease for 34 months. Of 17 patients with Stage IV disease, 10 have been free of disease for an average period of 1 year [84].

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It is still too early to draw any conclusions from these preliminary results. There is a great need for prospective randomized trials including a control arm without chemotherapy.

PROSTATE CANCER

Clinical and pathological staging

The prognosis of carcinoma of the prostate depends on the extent of the disease, and also on the histological grade of malignancy. Two clinical staging systems are in use at present: i.e. the TNM classification [57] (T1-T4, N1-N4, and M1) and the American classifications (Stage I–IV or Stage A–D). These classifications take note of prognostic features such as intracapsular (T1–T2, Stage I–II, Stage A–B) or extracapsular (T3–T4, Stage III, Stage C) tumor and of lymph node metastases (N1–N4, Stage III, Stage C) and distant metastases (M1, Stage IV, Stage D).

The histological degree of malignancy is classified G1 (high degree of differentiation), G2 (medium degree of differentiation), and G3 (low degree of differentiation or undifferentiated tumor). The poorly differentiated tumors are found to behave in a more aggressive manner than well-differentiated tumors. Five-year survival data show that patients with Stage I disease have a life expectancy comparable to age-matched controls, provided the tumor does not show a low degree of differentiation. The five-year survival rate for Stage II, III and IV disease is about 70%, 50% and 25%, respectively [10].

Hormonal therapy

In patients with advanced disease, hormonal manipulation with estrogens or orchietomy has been the treatment of choice [10]. Early studies of the Veterans Administration Cooperative Urological Research Group (VACURG) demonstrated that orchietomy and/or estrogen therapy in Stage III and IV patients did not improve the overall survival. Although estrogen therapy decreased the number of deaths from cancer, the daily use of 5 mg diethylstilbestrol (DES) increased the number of deaths from cardiovascular complications. The results of a later study showed that 1 mg DES was as effective as the 5 mg dose in preventing cancer deaths and yet caused less cardiovascular complications [10]. In updating the results of the first VACURG study, Jordan and Byar [85] concluded that estrogen (5 mg DES) is more effective than orchietomy in preventing deaths from cancer. Besides, the addition of orchietomy does not offer any advantage over estrogen therapy alone. It was advised that treatment should be withheld until it is required for relief of symptoms or because of progression of the disease. Estrogen therapy gives palliation of symptoms in 70–80% of the patients and objective regression of tumor in 30–40%, including the less than 50% responses. Several estrogens with equal response rates are available for clinical use (see Chapter 9).

Compounds consisting of a cytotoxic agent linked to a steroid have been
designed to carry an antitumor agent as an inactive complex to the steroid-dependent tissue of the prostate, where the cytotoxic drug would be specifically released. There are two examples to be discussed, i.e. estramustine phosphate [86–89] and prednimustine [90, 91]. A critical review of the available data shows that the objective response rate does not exceed 20%, including patients with less than 50% tumor regression. The combination of these drugs does not improve the results [91].

Hormonal therapies including progestogens [92–94], anti-androgens [95, 96] and medical adrenalectomy [97] are under investigation, but the reported results are poor. There is no place for these therapies in the primary treatment of prostate cancer.

Single-agent chemotherapy

Cytotoxic chemotherapy has been inadequately evaluated in patients with prostatic cancer, due to poorly defined criteria of response, staging difficulties, and the small number of patients in several studies.

Hydroxyurea has been investigated by two workers [103, 104]. Partial remissions were observed in 18/35 (51%) patients, indicating that this drug needs further evaluation.

Co-operative randomized studies have indicated that single-agent chemotherapy with adriamycin, cyclophosphamide and 5-fluorouracil can induce partial remissions ($\geq 50\%$ tumor regression) in hormone resistant patients (Table 6) [98–101]. Of these drugs, adriamycin is the most effective with a partial response rate of 27% [99].

Cisplatin has been evaluated by three investigators [48, 69, 70]. Two of them [69, 70] achieved similar results with a partial remission rate of 12–19% and a remission duration ranging from 4–15 weeks. The third investigator [48] achieved 31% partial remissions with an average duration of 30 weeks. It is of importance to recognize that the latter series consisted predominantly of patients with soft tissue indicator lesions.

In a small series of 10 patients, lomustine (CCNU) yielded 40% partial responses [101], suggesting that this may be an active drug.

Streptozotocin [101], procarbazine [101] and melphalan [102, 103] have been reported to be ineffective.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Remissions*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>35</td>
<td>18</td>
<td>51</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>26</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>53</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>60</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

* Predominantly partial remissions, meaning more than 50% tumor regression.
### Table 7. Combination chemotherapy in advanced prostatic cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Remissions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADM + CTX</td>
<td>18</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>ADM + CTX</td>
<td>15</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>ADM + CTX + MTX (CAM)</td>
<td>12</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>ADM + DDP</td>
<td>17</td>
<td>9</td>
<td>53</td>
</tr>
<tr>
<td>VCR + MTX + Pred + L-PAM + 5-FU</td>
<td>25</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

ADM = adriamycin; CTX = cyclophosphamide; MTX = methotrexate; DDP = cisplatin; VCR = vincristine; Pred = prednisone; L-PAM = melphalan; 5-FU = 5-fluorouracil.

### Combination chemotherapy

Several combinations have been reported effective (Table 7). However, none of these studies have been randomized and none concerns more than 25 patients.

There have been two recent reports on the effect of the combination of adriamycin and cyclophosphamide [105, 106]. The remission rates were 33% and 6% in 18 and 15 patients, respectively. Because these reports concern abstracts with limited data, the difference of remission rates is difficult to explain. In any case, this combination does not seem to offer any advantage over adriamycin as a single agent.

With the addition of methotrexate to adriamycin and cyclophosphamide 9/12 (75%) remissions have been reported [107]. These included 2 complete remissions. Only 4 patients survived more than one year.

The preliminary results reported by Perloff [108] indicate 9/17 (53%) partial remissions with the combination of adriamycin and cisplatin. Five of the responders relapsed within one year. Follow-up in the remaining 4 responders was less than 9 months.

The combination of vincristine, methotrexate, prednisone, melphalan, and 5-fluorouracil yielded 5/25 (20%) partial remissions [109]. The average survival of these patients was 63 weeks as compared with 42 weeks for patients with progressive disease. The results would probably have been the same without melphalan, since this agent has been reported inactive [102, 103].

Presently, there is no evidence that combination chemotherapy in prostate cancer is better than single-agent chemotherapy.

### RENAL CELL CARCINOMA

The prognosis of renal cell carcinoma is particularly poor when there is tumor ingrowth into the veins and an ESR above 30 mm. These indicators are more specifically related to the prognosis than the TNM (T1–T4, N1–N4, M1) and histopathological (G1–G3) classifications, taking note of extension of the primary tumor through the capsule (T3–T4), the extent of lymph node metastases and distant metastases, and the histological degree of tumor differentiation.
The preponderance of males among patients showing spontaneous regression of metastases suggests a hormonal influence on the tumor growth [12]. Progestational hormonal treatment of advanced renal cell cancer has resulted in response rates ranging from 0–26% [110, 111]. A survey of the world literature yields an average response rate of 8% [13].

Androgens led to regression of metastases in 3% of the cases and a combination of progestins and androgens was effective in 8.3%. The overall survival from the start of hormonal therapy is less than half a year [11–13]. These figures indicate that there is little or no support for the use of hormonal therapy on a routine basis.

Many anti-neoplastic drugs have been employed, both as single agents [112–116] and in combinations [14, 117, 118] for the treatment of metastatic renal cell carcinoma. No single-agent, combination chemotherapy regime or hormonal-chemotherapy combination is more active than vinblastine alone, which has a 33/135 (25%) response rate [115].

Immunotherapy [115, 119] of advanced renal cell carcinoma is under investigation, but has not yielded promising results so far.

PENIS CARCINOMA

Lymphogenic metastatic dispersion occurs primarily to the inguinal lymph nodes. The TNM classification takes note of unilateral and bilateral movable lymph nodes (N1–N2) and of fixed lymph node metastases (N3). Staging of the primary tumor depends on the local extension (T1–T3) or the invasion in neighboring structures (T4).

Surgical amputation and regional lymph node dissection give about 50% 3–5-year survival. There are very few data on chemotherapy of advanced carcinoma of the penis. In a non-randomized Japanese study the 5-year survival was 50% in a bleomycin-treated group of 24 patients and 73% for 66 patients who had been treated with bleomycin and radiotherapy, with or without surgery [120]. Unfortunately, the extent of the disease was not specified for the majority of the reported patients. Other investigators have also reported dramatic responses with the combination of bleomycin and radiotherapy without surgery in such patients [121]. Bleomycin alone may be as effective as in combination with radiotherapy. Single-agent treatment with cisplatin yielded a remission in 5 out of 9 patients [48, 69] (see Chapter 6, Table 1). It thus appears that bleomycin and cisplatin may be active in the treatment of penile cancer.

CONCLUSIONS

Many articles on chemotherapy for advanced non-seminomas appeared in 1977–1978. The effectiveness of combination chemotherapy, with response rates of 60–100%, has been well established. The most important components of these combinations are vinblastine, bleomycin and cisplatin. The value of the multimodal approach has been emphasized for patients with
Stage III disease, particularly the role of reductive surgery in conjunction with chemotherapy. Retroperitoneal lymph node dissection appears to be the approach of choice for patients with clinical Stage II disease, not only to achieve adequate pathological staging, but also as part of multimodality treatment. There is no common opinion as to the approach of Stage I disease. There is a tendency to wait and give chemotherapy as soon as there is a rise in tumor markers. The value of monitoring of tumor markers is emphasized more and more. Several important questions to be studied have emerged: (1) How can the complete remission rate in Stage III disease be further increased? (2) Can the dose of antineoplastic agents, in particular that of vinblastine, be reduced in patients with sensitive tumors in order to reduce toxicity and to permit the addition of other drugs to the combinations in use? (3) What is the role of maintenance chemotherapy after a complete remission has been achieved? (4) At what time in Stage III disease should reductive surgery be applied? (5) What is the role of radiotherapy for patients with non-seminomas in Stages I and II? The answers to these questions can only be obtained by controlled cooperative studies.

Except for superficially growing bladder tumors, the overall survival of patients with bladder cancer is poor, with a 5-year survival of 25–50% after surgery or radiotherapy. In cases with a superficial tumor, the patient often suffers severe stress, due to repeated cytocoscopies and local surgical treatment for recurrent tumor. Therefore, attempts are being made to improve the results by the topical use of chemotherapeutic agents for the prevention or the treatment of recurrent disease. For this purpose, thiorectop has been demonstrated to be of value, while other drugs are still under investigation. With a few exceptions, single-drug chemotherapy and combination chemotherapy have been poorly evaluated. Cisplatin, methotrexate, and adriamycin are the most active drugs in the treatment of advanced bladder cancer.

Few studies have been done on adjuvant chemotherapy after cystectomy or radical radiotherapy, and no conclusions can yet be drawn. It is probably justifiable to investigate cisplatin and adriamycin in an adjuvant setting.

Treatment of advanced prostatic cancer is still yielding poor results. Hormonal treatment barely prolongs the overall survival and carries the risk of cardiovascular complications. As a result, estrogen therapy should be withheld until progression of the tumor occurs. Cytotoxic chemotherapy has not been adequately evaluated. The reported results are often highly divergent, mainly because of differences in the definition of response. However, the evaluation of cytotoxic drugs in the treatment of prostatic cancer is in progress and some of these drugs seem promising.

The hormonal and chemotherapeutic treatment of metastasized renal cell cancer still gives poor results. Advancement in the treatment of this type of cancer depends at present on a more intensive and thorough evaluation of inadequately evaluated drugs and development of new drugs. Further investigation of both specific and non-specific immunotherapy seems warranted.

As yet, no prospective randomized clinical trials have been performed on penile cancer, which means that no firm conclusions can be drawn about the role of any of the three treatment modalities now in use. Indications have been obtained that cisplatin and bleomycin are active drugs in this disease.
At present, it seems justifiable to advise bleomycin and radiotherapy for the treatment of patients with penile cancer in all stages of the disease.

REFERENCES


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