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Chemotherapy of advanced transitional cell carcinoma of the uroepithelium

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Summary. *Activity has been demonstrated for both single agents and combination chemotherapy in advanced transitional cell carinoma of the uroepithelium. Regimens are palliative; duration of response has been modest, usually ranging from 3 to 8 months. There are few complete responders; occasional patients remain disease-free at 1 and 2 years.*

Among the single agents, cisplatin (33% response rate in 188 patients thus far reported in the literature) and methotrexate (29% response rate) are among the best studied and perhaps most active single agents. Substantial activity is also seen for cyclophosphamide (31%), doxorubicin (23%), 5-fluorouracil (35%), and mitomycin C (21%). VM-26 and vincristine appear to have activtiy, but relatively few patients have been treated.

Response rates to combination chemotherapy, including cisplatin + doxorubicin, cisplatin + cyclophosphamide, and cisplatin + doxorubicin + cyclophosphamide, have ranged from 12% to 78%. Non-platinum-based combination regimens have also been studied, with response rates ranging from 14% to 50%.

The large number of active agents, together with the occasional occurrence of a relatively durable complete response, raises hopes that more active combinations will be found and that the current surgical adjuvant trials will be positive in this disease.

Introduction

Although the response rates to chemotherapeutic agents in bladder cancer are comparable to those for breast cancer and other chemo-responsive solid tumors, chemotherapy has not been as extensively explored in bladder cancer. The reasons are multiple: First, bladder cancer is a relatively uncommon tumor; since the overall incidence figures include superficial tumors which infrequently become invasive, only a small fraction of incident cases present with or develop metastatic disease. Second, potentially effective drugs cannot be used in many patients with metastatic disease because of the compromise in renal function that is often found in patients with bladder, renal pelvic, or ureteral cancer. Third, the time from documentation of metastatic disease in bladder cancer until death is quite short for most patients; in one series the median time from diagnosis of metastases until death was only 3.0 months [3]. Thus many of the patients are already quite debilitated at the time of diagnosis of metastatic disease and cannot tolerate trials of chemotherapeutic agents. Fourth, many patients have advanced regional disease alone. Prior to the era of CT scanning it was very difficult to obtain a quantitative response in these patients, which again decreased the pool of patients available for study. Fifth, there is a difference in chemotherapeutic responsiveness of local and metastatic disease, requiring larger numbers of patients for adequate study of the disease. These problems, superimposed on the usual problems in chemotherapeutic trials (heterogeneous population with respect to prior treatment, age, functional status, etc.), explain the relative paucity of data on bladder cancer chemotherapy.

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Single-agent chemotherapy

A number of chemotherapeutic agents have shown activity in metastatic bladder cancer. Cyclophosphamide, doxorubicin, 5-fluorouracil, methotrexate, and cisplatin have all been studied in more than 50 patients and appear to have activity against advanced transitional cell carcinoma. Vinblastine and mitomycin C also appear to have activity, although the number of patients studied is smaller.

Cyclophosphamide is one of the extensively studied agents. Initially high response rates were reported in a number of small series. However, when these were recently reviewed by Yagoda et al. [50], only two of 26 patients appeared to meet objective criteria of partial response. Thus, although a large number of patients have been studied with cyclophosphamide as a single agent, and this drug has been incorporated into many combination regimens, the activity of cyclophosphamide remains uncertain.

Although most investigators agree that doxorubicin has activity in bladder cancer, the degree of activity has been questioned. Although initial response rates as high as 35% have been reported [8], more recent studies have shown more discouraging response rates in the 20% range. Nonetheless, it appears that doxorubicin has activity. Schedule and dose may be important factors for optimal effect [51].

A large fraction of the patients reported to respond to 5-fluorouracil were treated in drug-oriented phase II trials [17, 25]. Although a large number of patients have been treated, most series contain under 25 patients; early series with 5-fluorouracil have not given adequate attention to the quality and character of response. In a randomized trial 5-fluorouracil

was not superior to placebo when used in the adjuvant setting [34].

Methotrexate has been utilized in a large number of patients with metastatic bladder cancer. Hall et al. reported a response rate of 10 of 28 (35%) in their review [18]. The Royal Marsden experience has been amplified by Turner [44], who reported on three different methotrexate schedules. There were three of 25 responses with the 50 mg every 2 weeks regimen, 12 of 23 responses with 100 mg every 2 weeks, and eight of 16 with 200 mg every 2 weeks (with leukovorin rescue). There were four complete responders in this series and one CR lasted 20+ months. The Memorial Sloan-Kettering experience [27] also demonstrated substantive activity for methotrexate (11 of 42, 26%). Patients without prior chemotherapy had a higher response rate (6 of 16, 38%), as did patients who received the lower dose without rescue (10 of 33, 30%).

Cisplatin has been widely utilized and has demonstrable activity in metastatic bladder cancer. Initial studies at Memorial Sloan-Kettering showed an overall response rate of 33%, with 10 of 21 responses in patients with prior chemotherapy [48]. Response rates of 37% at Roswell Park [23], nine of 27 reported by Soloway et al. [41], and nine of 21 by Herr [19] appeared to confirm the high response rate. One study by the National Bladder Cancer Collaborative Group demonstrated a lower response rate in nine of 46 evaluable patients. As with methotrexate, complete responders have occasionally been observed [19], with durations exceeding 1 year in these complete responders.

In addition to these agents, a number of other drugs appear to have activity in bladder cancer. Vinblastine responses have been reported in small series of patients by Holland et al. [20] and Pavone-Macaluso [31]. Blumenreich et al. [5] noted responses in five of 28 patients (18%), all of whom had received prior chemotherapy. Hexamethylmelamine activity has been reported, with an overall response rate of 36% [4, 47]. A number of these patients had squamous cell carcinoma of the bladder. Mitomycin C also appears to have activity with an overall response rate of 21% in 48 evaluable patients [11, 28, 31]. Although initial reports of activity with VP-16 and VM-26 were encouraging, more recent studies have demonstrated minimal activty.

Table 1 summarizes the published results obtained so far with single-agent chemotherapy in bladder cancer.

Table 1. Single-agent activity in advanced bladder carcinoma

Drug	Number of patients	% response	References
Bleomycin	58	9	15
Cyclophosphamide	98	31	10, 14, 24, 49
Doxorubicin	235+	23	8, 10
5-Fluorouracil	75+	35	8
Hexamethylmelamine	35	36	4, 47
Methotrexate	140	39	1, 2, 6, 27, 31, 44
Mitomycin C	48	21	11, 28, 31
Neocarzinostatin	18	6	26
	17	70	37
cis-Platinum	188	33	12, 23, 33, 36, 40, 41, 48
PALA	12	0	49
VP-16-213	12	0	29, 49
VM-26	29	20	22, 32, 49
Vinblastine	35	17	5, 31
Vincristine	11	27	20, 31

Table 2. *cis*-Platinum-containing combination regimens for advanced bladder carcinoma

Drug	Number of patients	Number responding	(%)	References
cis-Platinum + cyclophosphamide	32	15	(47)	48
cis-Platinum + cyclophosphamide	47	6	(13)	12
cis-Platinum + doxorubicin	26	14	(54)	48
cis-platinum + doxorubicin	36	13	(36)	16
cis-Platinum + cyclophosphamide + doxorubicin	50	26	(52)	38
cis-Platinum + cyclophosphamide + doxorubicin	23	19	(83)	21
cis-Platinum + cyclophosphamide + doxorubicin	15	2	(13)	7
cis-Platinum + cyclophosphamide + doxorubicin	12	10	(90)	42
cis-Platinum + doxorubicin + 5-fluorouracil	16	10	(63)	45
cis-Platinum + doxorubicin + 5-fluorouracil	39	18	(46)	46

Table 3. Combination regimens for advanced bladder carcinoma (non-platinum-containing)

Drug	Number of patients	Number responding	(%)	References
Doxorubicin + cyclophosphamide	18	9	(50)	24
Doxorubicin + cyclophosphamide	17	3	(17)	50
Doxorubicin + 5-fluorouracil	85	35	(41)	9, 13
Doxorubicin + VM-26	27	5	(19)	35
Doxorubicin + cyclophosphamide + 5-fluorouracil	21	3	(14)	39
Doxorubicin + cyclophosphamide + methotrexate	26	10	(38)	43
Cyclophosphamide + hydroxyurea + vinblastine + vincristine	18	4	(22)	30

Combination chemotherapy

There is no study that has shown definitive advantage for combination chemotherapy in metastatic bladder carcinoma. Nonetheless, a large number of chemotherapeutic trials have been undertaken and many have demonstrated rather dramatic activity. Ciplatinum is the most widely used drug, which is often combined with doxorubicin or cyclophosphamide. Overall, over 300 patients have been treated with combination chemotherapy regimes. Response rates have ranged from 12% to 83% . Many responses have been in the 50% range. Table 2 lists the combination regimens in reports with more than 10 evaluable patients. Importantly, even though response rates are high, the duration of response has not extended beyond the 6- to 9-month range for these combinations. Table 3 lists selected studies of non-platinum-based combination chemotherapy reported in bladder cancer. Again, response rates tend to have been high in these studies, although it is difficult to make comparisons between these combination studies and single-agent chemotherapy.

Conclusions

Among single agents in bladder cancer, cisplatinum, and methotrexate appear to have the most activity. Doxorubicin has significant activity, as do vinblastine and mitomycin C. Some of these agents will need further trials to define the extent and durability of their activity in bladder cancer. The efficacy of two agents which have been studied extensively in bladder cancer is still uncertain: 5-fluorouracil and cyclophosphamide. These agents need to be restudied in light of current definitions of response.

Combination chemotherapy has no demonstrable benefit beyond single-agent chemotherapy and should not be routinely employed outside a study situation. There is no demonstrated role for adjuvant chemotherapy in bladder cancer, although a number of trials are now ongoing to define the role of chemotherapy as an adjunctive to invasive carcinomas of the bladder.

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