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The chemotherapy of advanced bladder cancer

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Summary. This paper traces the development of the use of chemotherapy in the management of advanced bladder carcinoma in Europe. A number of agents, including cisplatin, methotrexate, vinblastine, adriamycin, fluorouracil and cyclophosphamide, have been investigated singly and in combination in phase II studies, and it is envisaged that an ideal combination chemotherapy regimen giving lasting complete response will ultimately be used along with limited ablative surgery in the management of localised advanced bladder cancer. Careful application of the increasing knowledge of the biology of transitional cell carcinoma and strict adherence to rigid criteria of response in the assessment of new agents appears at last to offer hope of an improvement in the prognosis of invasive bladder cancer.

Many different chemotherapeutic agents have been studied in advanced bladder cancer, in a variety of dose schedules. They have been used independently, in combination, and as adjuvant therapy to surgery or radiotherapy. This paper covers predominantly the European experience and is concerned with the activities of the European Organisation for Research and Treatment of Cancer and its Chemotherapy Committee, which has been responsible for a number of the major European studies of chemotherapy in patients with advanced bladder cancer.

The use of chemotherapeutic agents in advanced bladder cancer started off in a somewhat haphazard manner. While not satisfied with the results of traditional therapy of cystectomy or radical radiotherapy, one of the major difficulties that urologists and medical oncologists laboured under, at first, was the fact that agents that were effective intravesically in the management of superficial bladder cancer were too toxic to be used systemically. In the early 1970s, in spite of what were then regarded as advances in surgical and radiotherapeutic techniques, two-thirds of patients with invasive bladder cancer were dying of their disease within 3 years of primary therapy. The addition of preoperative irradiation lowered this figure by very little, improving the prognosis by only 5%–10% [25] (*Tables* 1, 2).

With a better understanding of the biology of solid tumour growth and following careful examination of the pattern of failure in patients subjected to cystectomy or radical radiotherapy, it was realised that chemotherapy would probably have to be used as adjuvant therapy for this disease, since it was unlikely that a chemotherapeutic agent sufficiently powerful to be curative in its own right would ever be discovered. Isaacs and Coffey [3] suggested in the late 1970s that chemotherapeutic agents were probably only capable of eliminating small collections of tumour cells of the order of 10^9 cells, i.e. less than 1 cm^3 in volume, and that chemotherapy should therefore be used for individual tumour masses of this size. Over half the patients who undergo cystectomy or radical radiotherapy for bladder cancer die of metastatic disease, and of these, local disease has been controlled in 40% [13]. This suggests that micrometastases are probably present at the time of the initial diagnosis though not visualised by standard imaging techniques. It is at this stage, i.e. when they are less than 1 cm^3 in volume, that these metastases would be sensitive to chemotherapy and that this therapy should be administered.

In the late 1970s the EORTC accepted the concept of chemotherapy as an adjuvant therapy and concluded that

Table 1. Cumulated results of cystectomy with and without preoperative radiotherapy for invasive bladder cancer [2, 10, 25, 26]

	Operative mortality	5-year survival
Partial cystectomy	≥ 4%	30%
Simple cystectomy	3%–10%	35%
Radical cystectomy	4%–12%	38%
Preoperative radiotherapy and cystectomy	4%– 9%	42%
Preoperative radiotherapy and radical cystectomy	3%–13%	43%

Table 2. Results obtained with radical radiotherapy at the Karolinska Institute [5]

Survival	Category			Grade	
	T_2	T_3	T_4	G_2	G_3
5 years	31	20	10	26	18
10 years	22	14	4	19	13

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there would be three phases in the development of its use in standard practice. The first phase would be devoted to finding effective agents; the second to checking that they would be acceptable when used alongside standard treatment modalities, such as surgery and radiotherapy; and in the third phase tests would be conducted to determine the correct scheduling of the modalities of treatment available for combination in order to achieve better cure rates and longer-lasting cures [18].

The first aim, then, was to define an active agent or agents, and if they were to be used for curative treatment they had to be agents yielding significant rates of complete and prolonged response when used in isolation. In 1975, when this search for effective agents was started, Carter and Wasserman [1] had identified three principal agents with response rates in the order of 25%–30%, viz. adriamycin, 5-fluorouricil, and mitomycin. In addition, Hall et al. [7] had confirmed that methotrexate was effective in patients with advanced disease. The response to these single agents was short-lived: around 3 months in most studies.

The first study carried out by the EORTC GU Group investigated a combination of 5-fluorouracil and adriamycin in doses of 500 mg/m^2 and 50 mg/m^2 administered at 3-weekly intervals for a minimum of four courses. This followed a study carried out in Yorkshire by Cross et al. [4], which had shown a 35% response rate. The EORTC study showed an overall response rate of 40%, with fewer than 10% complete responses [6]. The average duration of response was 3 months.

A diversion followed when an attempt was made to carry out a phase III study of this regimen against adriamycin alone, but it was found impossible to recruit a sufficient number of patients and the study was abandoned. These early results may be a little misleading, as the criteria of response were variable and certainly less precise than in later studies. Because of this, at this stage it was decided to pursue the search for an effective agent or agents using a standard phase II format. The EORTC GU Group Chemotherapy Committee therefore evolved a master protocol for the investigation of new agents in advanced bladder cancer. The inclusion criteria for patients are clearly defined, and strict response criteria are also used Table 3.

In 1977 Yagoda [27] described 8 partial responses in 23 patients treated with cisplatin alone. Other workers confirmed that this was an effective agent and Peters and O'Neill [12] and Soloway [20] have published other important studies of this agent. Subsequently it was suggested that the addition of Cytoxan (cyclophosphamide) to cisplatin improved the complete response rate.

The EORTC then carried out their second phase II study, examining the use of cyclophosphamide, adriamycin and cisplatinum (cyclophosphamide 400 mg/m^2, adriamycin 40 mg/m^2, and CDDP 40 mg/m^2 given every 3 weeks over a period of 6 months. There were 42 evaluable patients; the complete response rate was 12% and the partial response rate, 28%. The duration of response was 5–7 months. The total response rate was thus, again, around 40%, and not significantly superior to that obtained with cisplatin alone [11].

At approximately the same time a study investigating vincristine as a single agent was also performed. Among 36 evaluable patients there were only 1 complete response and 3 partial responses; abdominal pain and neurological complications were common, and it was concluded that this agent had no significant or useful activity in bladder cancer [15].

Table 3. Criteria of inclusion for patients to master protocol of Phase II study of chemotherapy in advanced bladder cancer, and criteria of response

Conditions for patient eligibility
Histologically proven transitional cell cancer of the urinary tract, including bladder, ureter and renal pelvis
Measurable distant metastases (M_1, stage IV)
1. Skin and subcutaneous metastases.
2. Superficial lymph nodes.
3. Lymph nodes in the mediastinum and in the retroperitoneal region if they can be measured by CT-scan. The initial diameters must be *greater then 3 cm* to allow reliable measurements during follow-up.
4. Liver metastases if they can be measured by CT scan or ultrasonic echography. The initial diameters must be *greater than 3 cm* to allow reliable measurements during follow-up.
5. Lung metastases.
Unresectable primary bladder cancer and pelvic recurrences only if the tumor can be measured by CT scan.
Performance status (WHO scale) of 0, 1 or 2.
Response criteria
A complete response will be defined as the complete disappearance of all objective parameters, determined by two observations not less than 4 weeks apart, with no new lesions having developed.
A partial response will be defined as at least a 50% reduction in the sum of the products of the two largest perpendicular diameters of all measurable lesions, determined by two observations not less than 4 weeks apart, with no new lesions having developed.
No change will be defined as a change of less than 50% reduction or less than 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions.
Progressive disease will be defined as an increase greater than 25% in the sum of the products of the two largest perpendicular diameters of all measurable lesions, *or* the appearance of new lesions.

In the next phase II study a combination of cisplatin and VM26 was investigated. The latter is an epipodophyllotoxin effective in isolation in advanced bladder cancer and possibly synergistic with cisplatin. This Protocol was followed in 41 evaluable patients and complete response was achieved by only 4 (10%), with partial response achieved by 17 (41%), giving an overall result little better than that with cisplatin alone. The median duration of response was 6 months [21].

By 1982 it had become evident from work in the USA [28] that the two most active agents in bladder cancer were methotrexate and cisplatin. Each separately gave response rates of 30%–35%, and it was anticipated – and indeed there was some theoretical justification for this – that together they might yield even better results, though the hazard of increased nephrotoxicity might be a major problem. With a maximum serum creatinine of 140 μmol/l it was felt it would be safe to give cisplatin at 70 mg/m^2 on day 1 with methotrexate 40 mg/m^2 on days 8 and 15. The results of this initial study (no. 30821) showed that among 35 evaluable patients there was a 23% complete response rate, the overall response rate being 46%. The median duration of response was 23 weeks for the partial responders and 64 weeks for the complete responders [22]. The regimen was toxic, however, mucositis, bone marrow toxicity,

Table 4. EORTC phase II studies

			Duration (years)			
			CR	PR	CR	PR
EORTC Group B	"Pilot"	ADM/5-FU	4/52	21/52	4/12	3/12
EORTC (J. R. Mulder, Rotterdam)	30771	CTX/ADM CDDP	5/42	12/42	7/12	5/12
EORTC	30797	VCR	1/36	3/36	7/12	3/12
EORTC (G. Stoter, Amsterdam)	30802	CDDP/VM26	4/41	17/41	8/12	4/12
EORTC (J. Childs, Leeds; B. Richards, York; G. Stoter, Amsterdam)	30821	CDDP/MTX 70 mg m^2/40 mg m^2 Day 1/days 8 & 15	8/35	17/35	15/12	6/12
EORTC	30823	Mitoxanthrone	0/28	0/28		
EORTC (G. Stoter, Amsterdam)	30842	CDDP/MTX 70 mg m^2/40 mg m^2 Day 1/days 1 & 15				

and renal toxicity being the most serious toxic effects. The scheduling of these drugs was further investigated in 1984 by Kaye [9], whose individual pharmacokinetic study in 5 patients, suggested that it was, in fact, safe to give cisplatin and methotrexate together on the 1st day of a cycle. He suggested that one of the reasons for the high nephrotoxicity of this EORTC regimen was that the nephrons had not recovered from the insult of cisplatin by the time methotrexate was administered on day 8.

The subsequent study (no. 30842) performed by the EORTC empoyed a regimen of cisplatin 70 mg/m^2 and methotrexate 40 mg/m^2 given on day 1 of the cycle, followed by methotrexate 40 mg/m^2 on day 15. The results of this study have not yet been published (G. Stoter 1986, personal communication, Table 4).

At the same time as these studies were being carried out, two second-line phase II studies investigating the activity of mitoxanthrone and TGU in advanced bladder cancer were started. The first study of mitoxanthrone showed it to be ineffective, there being no responses in 28 adequately treated patients; and the study with TGU was abandoned because of overwhelming toxicity with no evidence of significant action in this group of patients [23].

Before coming right up to date with the phase II studies currently in progress in the EORTC, it is important to mention two studies of adjuvant chemotherapy that were carried out in 1977 and 1978; this is important not only because of their negative results, but also because they influenced our subsequent approach to advanced bladder cancer.

The first adjuvant study was carried out in Yorkshire and compared radical radiotherapy plus cytotoxic therapy, in this case adriamycin and 5-fluorouricil, with radical radiotherapy alone. A total of 110 evaluable patients were investigated in this study, and the conclusion was that chemotherapy, or at least this particular regimen, when added to radiotherapy did not improve the overall survival rate or the time to progression of disease. There was appreciable toxicity, and in particular complete alopenia [16] (Fig. 1).

In 1978 a further study was embarked upon by the EORTC to find whether 5-fluorouracil and adriamycin,

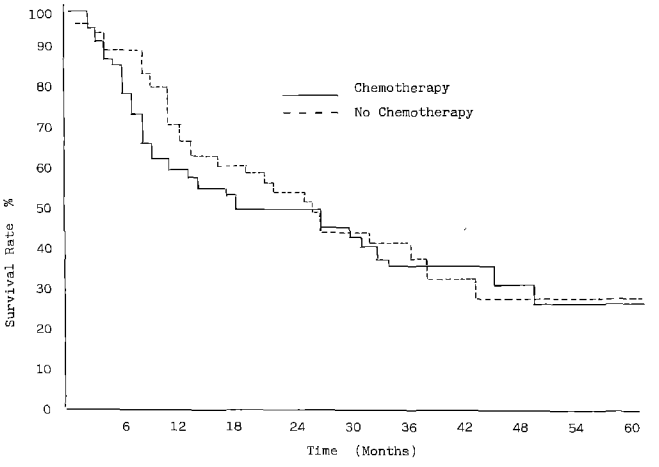

Fig. 1. Deaths from any cause in YUCRG T_3 Bladder Study

which again seemed to be the most active combination available at that time, improved the prognosis in patients with $T_3N_{1-2}M_0$ disease treated with cystectomy with or without preoperative irradiation therapy. The interesting point about this protocol was that it proved impossible to recruit patients. In particular, it was very difficult to find patients who had undergone cystectomy with or without irradiation therapy who were fit enough, or willing, to undergo chemotherapy [18]. At this point it was interesting to note that a protocol launched by the NBCC GPA, with cisplatin used as adjuvant therapy to preoperative irradiation and cystectomy (protocol 7), led to a very high rate of ineligibility and lack of evaluability in the final numbers achieved. A total of 423 patients had been evaluated by the end of 1982, only 199 of whom were eligible according to the protocol. After cystectomy only 84 were randomised, and ultimately fewer than 30 patients completed the chemotherapy. Therefore, no meaningful results were obtained from this study, and Prout [14] concluded in 1984 that this was not the correct use of chemotherapy; the EORTC agreed with this view.

About the same time as these two adjuvant studies were foundering a slightly different approach to the management of advanced bladder cancer was being adopted in Belgium and subsequently in the northeast of England. Soquet [19] saw chemotherapy as a possible means of avoiding multating radical surgery in T_3 bladder tumours and instituted a regimen of local surgery, either partial cystectomy or transurethral resection of the primary tumour, followed by methotrexate 1–2 g with folinic acid rescue. This was given 3-weekly for a period of 6 months. His results of 90% survival at 2 years in 44 patients were astonishing, and even though the 3-year survival was lower it was still better than any so far achieved with conventional therapy. This regimen was followed in an identical study in the north of England with the following results [8] (Table 5). At 3 years 52% survived; some had had superficial recurrences but none had developed further invasive lesion. These results were better than those of cystectomy or radiotherapy alone and marginally better than those of combination therapy.

By the end of 1984 it had been shown that chemotherapy plus local surgery yielded as good results as standard radical ablative therapy. A reasonably active chemotherapeutic regimen had been identified in methotrexate and cisplatin. Veronesi [24] suggested that considering the biological behaviour of bladder cancer, and specifically the finding that a large number of patients died of metastatic disease with their local disease controlled, it would be logical to use chemotherapy as the primary treatment. In Europe this possibility is being activitely studied both by the Medical Research Council in the UK and by the EORTC. Both studies are currently being conducted with a combination of methotrexate and cisplatin, and the definitive debulking or operative procedure in both is left unspecified (Table 6). Many of us with experience of the Socquet regimen and radical transurethral resection for invasive bladder tumours are favouring this as a definitive secondary therapy after chemotherapy. Although only anecdotal, the results so far seem very encouraging.

Meanwhile, the search for yet more effective combinations of chemotherapeutic agents continues. At the Sloan-Kettering and San Paulo Schools of Medicine, MVAC (methotrexate + vincristine + adriamycin + cyclophosphamide) is being studied in advanced bladder cancer. With this combination as primary treatment in T_3 carcinoma of the bladder Simon has reported [17] a 75% overall response with 12 patients, and 33% of these have had a complete response. In the Sloan-Kettering series, although there was an initial 7% mortality from chemotherapeutic toxicity, the response rate is similar in the 45 patients so far studied. The complete response rate is 40%, with an overall response of 67%. The mean duration of response is greater than 1 year [21].

In Yorkshire interest has centred on the second-generation adriamycin compound, 4-epirubicin. In a study of primary $T_{3-4}M_0N+$ cancer an overall response rate of 4/9 has been achieved, with complete response in 2 (W. Jones 1986, personal communication). Toxicity with this compound is minimal, being far lower than with the MVAC regimen or even adriamycin alone. In the next EORTC phase II study an attempt will be made to answer the question as to whether the addition of vinblastine to the effective combination of cisplatin and methotrexate improves the response rate in metastatic transitional cell carcinoma of the bladder. This will be the first-line chemotherapy study, but a second-line study investigating 4-epirubicin in patients with measurable metastatic transitional cell carcinoma of the bladder is also shortly to be started.

Table 5. Comparison of survival of patients with T_3 carcinoma of bladder following various treatments (%)

	1 year	3 years	5 years
Institute of Urology 1982: Radiotherapy	54	44	33
YUCRG: Radiotherapy	70	54	37
Institute of Urology: Radiotherapy and cystectomy	63	50	45
Socquet: Partial cystectomy/methotrexate	98	85	85
North Eastern Study: TUR and Methotrexate	81	60	52

Table 7. Plan of tentatively planned therapeutic regimen

TURB	Chemo RT ? 3 cycles ? Cisplatin Methotrexate Vinblastine ? 4-epirubicin	REASSESS – CR	–	Follow-up
		– PR	Local surgery	Follow-up
		– NC		
		– PD		Radiotherapy

TURB, transurethral resection of the bladder

Table 6. Schema for protocol 30851: methotrexate and cisplatinum in T_3 bladder tumor

Cisplatin	70 mg/m² i.v. day 1	Every 3 weeks	2 COURSES	PR CR	+2 Courses; second evaluation
Methotrexate	40 mg/m² i.v. days 8–15			PD SD	Stop; optional therapy

From the European viewpoint the future management of T_3 TCCB will follow the pattern that now seems to be emerging as the most efficient method of treating advanced bladder cancer. Front-line chemotherapy with a combination of methotrexate, cisplatin and possibly 4-epirubicin or vinblastine will be followed by a debulking procedure, probably of the local or locoregional variety without radical ablation of pelvic lymph nodes, since no clear advantage has been demonstrated for this more radical procedure. This still leaves radiotherapy to be used for salvage. As far as further research is concerned, we will continue to look for increasingly more active and less toxic regimens by continuing the series of phase II studies already embarked upon and to attempt to perfect the staging of advanced bladder cancer to avoid the high mortality with missed metastases. Invasive bladder cancer still carries a prohibitive mortality, and it is clear that we can only hope to improve this by very careful application of all available treatment modalities.

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