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GUEST EDITORIAL

Chemotherapy for advanced bladder cancer: 'Midsummer Night's Dream' or 'Much Ado About Nothing'?

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The past decade has seen important progress in our understanding of the biology and management of bladder cancer, one of the most common malignancies in Western society. Important concepts have emerged regarding the functional heterogeneity of bladder tumours that appear similar under the light microscope, but which are composed of subpopulations of cells with different metastatic and invasive properties (Brown *et al.*, 1990). Extensive data have been produced with regard to newer and more accurate indices of prognosis, including the expression of epidermal growth factor receptor, DNA content, marker chromosomes and the expression of oncogenes, as reviewed in detail elsewhere (Raghavan *et al.*, 1990).

However, it has become increasingly clear that, despite the best available treatment, approximately 50 per cent of patients presenting with invasive transitional cell carcinoma will die within 5 years (Skinner & Lieskovsky, 1984; Gospodarowicz *et al.*, 1989). The traditional determinants of adverse prognosis include advanced tumour stage, size, high grade, and the presence of hydronephrosis (Shipley *et al.*, 1984; Gospodarowicz *et al.*, 1989), and studies are in progress to determine the relative utility of these factors, compared to the more recently introduced determinants listed above.

Patients with loco-regional recurrence or distant metastases have been treated with systemic cytotoxics, occasionally achieving dramatic remissions. As a result, patients with invasive, but clinically non-metastatic bladder cancer have more recently been treated with initial systemic chemotherapy as part of planned definitive treatment in an attempt to improve cure rates. Although there have been many early reports of high response rates, it has not been clear whether real progress has been made with improvement in survival. Thus it is timely to discuss the available data regarding the use of chemotherapy for locally advanced, recurrent and metastatic bladder cancer.

Chemotherapy for metastatic and recurrent bladder cancer

For more than 30 years, cytotoxic chemotherapy has undergone evaluation in the management of bladder cancer (Wilson, 1960; Carter & Wasserman, 1975; Young & Garnick, 1988; Tonkin & Tannock, 1988). The data from the early phase clinical trials have reflected the criteria of assessment of outcome and the techniques of supportive care as they have evolved. Thus, for any cytotoxic drug or combination of drugs, a broad range of response rates and levels of toxicity have been reported. When criteria of assessment that would have been acceptable by current standards (Van Oosterom *et al.*, 1986; Tonking & Tannock, 1988) have been used, it has been clear that objective response rates of 20–35 per cent can be achieved in metastatic or recurrent bladder, or urothelial tract tumours treated with cisplatin, doxorubicin, methotrexate, mitomycin or cyclophosphamide, used as single agents (Young & Garnick, 1988; Tonkin & Tannock, 1988). When such drugs have been used in this fashion in typical elderly patients with bladder cancer, the toxicity has been manageable, with nausea and mild-to-moderate myelosuppression being the predominant features.

Since 1977, many uncontrolled trials have yielded high objective response rates and a broad range of toxicity when combination chemotherapy regimens have been applied to this problem. Whether high objective response rates actually translate into a survival benefit has not been addressed in these trials. However, single agent chemotherapy has been compared with combination regimens in several randomised trials (Table I), most of which have failed to reveal a statistically significant or clinically relevant survival benefit from combination chemotherapy. Moreover, in these trials, combination regimens have caused significantly greater levels of toxicity (Soloway *et al.*, 1983; Khandekar *et al.*, 1985; Troner *et al.*, 1987; Hillcoat *et al.*, 1989). Despite the lack of evidence supporting the use of combination regimens, investigators have continued to develop more intricate (and toxic) regimens, predicated on the hope that high response rates would ultimately translate into improved survival. Of particular importance are two studies with clearly defined criteria of response and toxicity, in which the combination of methotrexate, cisplatin and vinblastine (with or without doxorubicin) – the CMV or MVAC regimens – have yielded reproducibly high response rates in primary tumours and in metastatic deposits (Meyers *et al.*, 1985; Sternberg *et al.*, 1985, 1988). Complete responses proved by biopsy have been noted in liver, bones, lungs, lymph nodes and soft tissue deposits (Sternberg *et al.*, 1988). Regrettably, the separate reporting of survival for responding and non-responding patients (Sternberg *et al.*, 1988) initially created the illusion that the problem of metastatic bladder cancer may have been solved (Olsson, 1987). However, with increased experience (Tannock *et al.*, 1989; Connor *et al.*, 1989; Sternberg *et al.*, 1989) it has become clear that a substantial proportion of tumours that respond to these regimens are ultimately destined to relapse, and that the percentage of patients who are

Table I Results of randomised trials of single agent and combination chemotherapy regimens for advanced bladder cancer.

Regimen	*No. of patients*	*Response rate*	*Median survival*	*Survival tail*	*First author of series*
Cy	59	20%	<12.0	<20%	Soloway[a]
CyC	50	12%	<12.0	<20%	
C	67	17%	6.0	<15%	Khandekar
CyDC	63	33%	7.3	<15%	
C	57	16%	5.0	<10%	Troner
CyDC	52	21%	7.0	<10%	
C	55	31%	7.2	<20%	Hillcoat
MC	53	45%	8.7	<20%	
C	110	9%	8.7	<30%?	Loehrer
MVDC	110	33%	12.6	<30%?	

[a]35% of randomised patients were ineligible; Cy: cyclosphosphamide; C: cisplatin; M: methotrexate; D: doxorubicin; V: vinblastine.

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potentially cured (20–30 per cent) would be lower than anticipated.

There has thus been a risk that these regimens would be abandoned and the search for a new panacea resumed (Connor *et al.*, 1989). However, a recently completed randomised trial, carried out by investigators in North America and Australia has set the situation into a more realistic perspective (Loehrer *et al.*, 1990). We compared outcomes in patients treated with single agent cisplatin (70 mg m^{-2}) and the so-called MVAC regimen, with the major endpoint being survival. Although the difference in reported median survival is only modest (8 *vs* 12 months), there is a statistically significant improvement throughout the survival curves when MVAC is used, but at the expense of a statistically significant increase in toxicity (Loehrer *et al.*, 1990). It thus appears that, for the younger and more robust patient, the best known outcome in metastatic bladder cancer can be achieved by the use of the MVAC regimen. Whether the CMV regimen (without doxorubicin, but with a higher dose of cisplatin) gives comparable results is not yet known as the appropriate comparative trial has not been effected. However, Logothetis *et al.* (1989) have shown that the MVAC regimen confers a survival benefit over the combination of cyclophosphamide, doxorubicin and cisplatin.

Of concern, a recent trial has reported that toxicity can be ameliorated by the replacement of cisplatin and doxorubicin, respectively, by their less toxic analogues, carboplatin and epirubicin, without loss of efficacy (Waxman *et al.*, 1989). However, the small treated sample consisted of a mixture of locally advanced, relapsed and metastatic tumours, and it is quite likely that a significant reduction in survival could have been missed. These data should be regarded with caution until the appropriate stratified, randomised trial has been carried out to define whether the patterns of toxicity and survival are different.

The provocative studies of Gabrilove *et al.* (1988), in which the use of colony stimulating factors reduced bone marrow and mucosal toxicity from the MVAC regimen, has given rise to new protocols in which the dose of MVAC is being escalated in the hope of increasing cure rates as a function of dose intensity. Once again, a randomised trial is planned to test this hypothesis.

Pre-emptive (neo-adjuvant) chemotherapy

In view of the relatively low cure rate from conventional treatment of invasive bladder cancer by cystectomy or radiotherapy (Skinner & Lieskovsky, 1984; Shipley *et al.*, 1984; Gospodarowicz *et al.*, 1989; Raghavan *et al.*, 1990), attempts have been made to develop innovative approaches to this problem. Based upon the high response rates recorded from the use of systemic chemotherapy for metastatic disease, several trials have been initiated to assess the efficacy of first-line chemotherapy as an adjunct to definitive treatment. The rationale for this approach has been reviewed in detail elsewhere (Raghavan, 1988).

Initially, a series of phase I and phase II clinical trials demonstrated that first-line intravenous or intra-arterial chemotherapy could be administered safely to the elderly population of patients with bladder cancer, and that few patients developed clinical evidence of metastases during the period of chemotherapy (Fagg *et al.*, 1984; Raghavan *et al.*, 1985; Jakse & Frommhold, 1985; Schulman *et al.*, 1985; Shipley *et al.*, 1988; Eapen *et al.*, 1989). Although it proved difficult to assess response in the primary tumour (Raghavan *et al.*, 1985; Van Oosterom *et al.*, 1986; Scher *et al.*, 1988), objective response rates of 60–80 per cent were recorded in most studies (Table II), although it is quite possible that the available literature was biased by editorial preference for 'positive' results (Simes, 1986). In general, patients tolerated the chemotherapy programmes with only modest side effects, and subsequent radiotherapy and/or cystectomy were not compromised by the use of chemotherapy. Provided that meticulous attention was paid to hydration schedules and anti-emetic regimens, even patients aged more than 70 years could be treated with safety, with sustained objective responses and with satisfactory quality of life when measured some years after treatment (Raghavan *et al.*, 1988). However, from these studies, it was not possible to determine the optimal approach to this treatment, and questions regarding dose, sequencing of treatment modalities, and delivery of cytotoxics (intravenous or intra-arterial) remained unresolved.

Moreover, these studies did not address the issue of improved survival, although the published results have erroneously been compared in some instances with historical controls. To date, only two randomised, controlled trials have been completed in which the impact of pre-emptive chemotherapy on survival has been assessed for patients with invasive bladder cancer. Shearer *et al.* (1988) showed no survival benefit from the use of initial intravenous methotrexate followed by radiotherapy and adjuvant methotrexate, compared to radiotherapy alone. In parallel studies in Australia and the West Midlands, the use of 2–3 doses of intravenous cisplatin (100 mg m^{-2}) did not appear to influence survival when radiotherapy was used as the definitive treatment (Raghavan *et al.*, 1989; Wallace *et al.* submitted),

Table II Results of clinical trials of pre-emptive chemotherapy for invasive bladder cancer

		Response rate after chemotherapy			*Response rate after all treatment*			*Median*	
First author	*Regimen*	*C.R. (%)*	*P.R. (%)*	*R.R. (%)*	*C.R. (%)*	*P.R. (%)*	*R.R. (%)*	*survival (months)*	*Actuarial long term survival*
Pre-emptive chemotherapy regimens									
Fagg	C	0	64	64	?	?	?	?	?
Kaye	CyMF	0	0	0	0	0	0	27	26% 3yr
Raghavan	C	–60–		60	–85–		85	32	40% 5yr
Scher[a]	MVDC	21	39	60	30	57	87[b]	?	?
Shearer	M	–	–	–	–	–	56	23	39% 3yr
	RT only	–	–	–	–	–	50	20	37% 3yr
Wallace	C	–	–	–	–	–	–	~24	39% 3yr
	RT only	–	–	–	–	–	–	~22	39% 3yr
Zincke[a]	MVDC	50	19	69	0	0	92	?	?
Concurrent chemotherapy regimens with radiotherapy									
Eapen	C	–	–	–	92	–	92	?	?
Rotman	F	–	–	–	50	42	92[c]	<30?	?
Shipley	C	–	–	–	–	–	76	30	30% 3yr,T3 25% 3yr,T4

[a]Cystectomy as definitive treatment; [b]Figures extrapolated from paper; 4 clinically staged and 5 pathologically staged with residual CA after Rx; [c]All T categories; prolonged treatment programme; relatively short follow up; C.R.: complete remission; P.R.: partial remission; R.R.: total remission rate; Rx: therapy; RT: radiotherapy.

although a difference of less than 20 per cent would have been missed because only 250 patients were randomised. Regrettably, the trials in the West Midlands and Australia closed prematurely, owing to lack of patient accrual (based on biases regarding the utility of the MVAC regimen and the changing application of cystectomy to the management of bladder cancer), and the results were analysed by the statistical technique of meta- or overview analysis (Sacks *et al.*, 1987).

In order to define more clearly the potential benefits of this approach, an international randomised controlled trial has been initiated, with participation by the Medical Research Council, European Organisation for Research and Treatment of Cancer, Australian Bladder Cancer Group, National Cancer Institute of Canada, Spanish Bladder Cancer Group and the Finnish National Bladder Cancer Study Group. This trial will test the survival impact of three cycles of CMV combination chemotherapy (Meyers *et al.*, 1985) when added to standard treatment (radiotherapy or cystectomy) for invasive, clinically non-metastatic bladder cancer. The use of the CMV regimen is predicated on the higher response rate documented for combination chemotherapy (Table I), and the concern that the negative trials of single agent chemotherapy may simply reflect inadequate chemotherapy regimens.

After nearly a decade of clinical investigation, the true role of pre-emptive chemotherapy has not been defined for invasive bladder cancer. There has been a wastage of resources (patients, cytotoxics and facilities) in the quest for a 'quantum leap forward', with the development of many small, innovative, but inevaluable pilot studies at the expense of accrual to well-designed, randomised trials. It is high time for this issue to be resolved by the completion of a well-structured trial with adequate accrual of patients, well defined endpoints and comparison with a conventionally treated control population. By contrast, the completion of such a trial in the management of metastatic disease has already defined more clearly the benefits and limitations of an intensive schedule of combination chemotherapy and has laid the foundation for future studies. As our understanding of mechanisms and predictors of resistance to cytotoxic chemotherapy evolves and our approach to the design and application of clinical trials improves, the emphasis of our work will hopefully shift from the empirical to the rational, and the rate of real progress will accelerate.

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