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Invited Review: Invasive Bladder Cancer – Possible Future Treatment Considerations

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Until recently, discussion on management of invasive bladder cancer has been limited to the relative merits of various forms of local treatment. In practical terms, this has meant debating the efficacy of radical radiotherapy [10, 52] compared with radiotherapy and cystectomy versus [3, 23, 51] radical cystectomy alone [34, 56], with advocates usually citing their own results and championing the benefits of their favoured approaches. Although local recurrence cannot be dismissed as unimportant, development of systemic disease constitutes the most common life-threatening aspect of this condition. Whatever form of local treatment is administered, at least 50% of patients die of metastases within five years, the majority succumbing within the first two years [46]. Because of this grim prospect, the possibility of effective systemic therapy, albeit limited, is very welcome and presently entrenched attitudes warrant reconsideration so that local forms of treatment alone assume less significance in the overall debate directed at treating the "whole patient".

Over the past decade, the management of superficial bladder cancer has changed considerably. Intravesical chemotherapy (i/ves) with cytotoxic drugs [24, 26, 28, 45] and bacillus Calmette Guèrin (BCG) [21, 29, 37] have become established as most effective methods for reducing the incidence of new occurrence formation. In addition, BCG administered intravesically [20, 35] is the preferred initial choice in the management of patients with widespread flat carcinoma in situ (cis). The strain of BCG is important, and a combination of intradermal and intravesical administration is probably more effective with fewer unwanted effects necessitating "isoniazid rescue" than higher dose intravesical therapy alone [36]. In 1983 Netto and Lemos reported excellent results using large doses of oral BCG for prophylaxis in 16 patients after transurethral resection of superficial bladder cancer followed for a median period of 39 months. Only one of these patients formed new occurrences compared to 80% of patients treated by transurethral resection of bladder tumour (TURBT) alone [39].

Another trial is in progress in the United States at present with an oral preparation of BCG and it will be very interesting to learn these results on completion of this study [30]. Netto and Lemos have also reported their experience with oral BCG given to patients with invasive bladder cancer citing a 70% response rate. Of six patients with grade III and clinical stage B2, two died with tumour and one died without tumour. Of three grade II tumours, one patient with clinical stage B2 died with tumour (one of each B1 and B2 remaining alive), and the one patient with grade 1, B1 tumour remained alive following oral BCG treatment. Follow-up was for 12–84 months with a median of 32 months [40]. The observation has been made as well that i/ves BCG therapy can induce regression of residual or unresected tumour tissue in addition to induced tumour in experimental animals [7, 31, 38, 42, 43] and recent preliminary reports of a therapeutic effect of BCG on muscle-invasive disease are highly suggestive in this regard too [14]. Currently, Lamm is studying 37 patients who had muscle invasive disease treated by a combination of i/ves and percutaneous BCG. These patients either refused or were considered unfit or unsuitable for cystectomy. Four patients had previously been given radiotherapy. With a median follow-up of 41 months, 32% are clear of disease and 43% are alive. A number of these patients has had partial cystectomy and most deaths in this study have been disease related [30]. At present a report is in press in which over 1,200 patients involved in trials with BCG and bladder cancer have been examined. Many of these patients received pelvic radiotherapy in addition to BCG treatment, yet only two patients have developed contracted bladders [30].

There is indirect evidence that BCG causes more than just a local irritative effect on the bladder as some sceptics assert. Monitoring of increased numbers of monocytes in the circulation following BCG administration [14, 32, 48] and a reduced immunogenic effect following isoniazid therapy for systemic effects of BCG therapy [36] support this belief, but failure of i/ves BCG to address carcinoma in situ in the lower ureters and prostatic ducts is perplexing

and seemingly contradictory [36]. For immunotherapy to be effective, tumour burden must be small and it is essential that an adequate dose of therapeutic agent be given [37]. Lack of recognition of these factors explains, at least in part, the failure of immunotherapy to live up to its high expectations in the past and its prejudiced consideration subsequently. As a consequence, it would seem that, if immunotherapy has a role in invasive bladder cancer, this role will probably be adjunctive. BCG is usually relatively non-toxic (apart from transient local irritative effects from i/ves administration) [36, 60] and may prove to be of value in combination with chemotherapy [1] and radiotherapy as both these forms of treatment have been reported to be immunosuppressive [44]. Since the recent identification of tumour associated antigens in bladder cancer [9, 11, 17], the long-cherished idea of immunotherapy with 'magic bullet' monoclonal antibodies has begun to be evaluated [13, 64]. It would seem that the number of courses is limited when mouse monoclonals are used and this may prove to be a considerable constraint. However, results of studies will be awaited with fascination.

Most attention in treatment of invasive bladder cancer systemically has been directed towards cytotoxic chemotherapy. Many studies have examined the role of chemotherapeutic agents alone, in combination with other drugs and as adjuncts to established forms of local treatment for both pelvic and metastatic disease [2, 5, 16, 18, 19, 22, 27, 33, 49, 55, 57, 62]. Overall, results have been disappointing and toxicity causing morbidity and mortality has complicated reports. The two most effective drugs examined to date have been cisplatinum and methotrexate, and until recently there was no evidence to support combination drug therapy as superior to single agent treatment [8, 41, 46, 58].

Using cycles of methotrexate, vinblastine, doxorubicin (adriamycin) and cisplatinum (MVAC) sequentially, Sternberg et al. reported complete clinical remission in 12 of 24 patients with metastatic or unresectable disease [61]. Importantly, metatastic tumour at all sites (including bone) responded to treatment, but toxicity was a problem with this regimen. Following surgical exploration, six out of the twelve have been deemed to be clear of disease pathologically at 7 to 14 months (two patients at 14 and 16 months refusing surgery). Of the other four, one had a microscopic focus in the prostate and another had a similarly sized deposit in perivesical fat, one a nodule in the chest, and yet another carcinoma in situ of the bladder.

There has been a number of studies in which chemotherapeutic agents have been used as adjuncts to established forms of local treatment in bladder cancer. Cisplatinum has been examined in this role – especially in combination with radiotherapy [25, 53, 59] – because of this drug's alleged radiosensitising action [50]. The best results to date have been reported by Raghavan et al. in which patients received two doses of high dose cisplatinum (100 mg per m^2) with a three week interval followed by definitive radiotherapy and/or cystectomy [47]. In a preliminary report 50 patients were examined. These included 7 B1, 31 B2 to C and 12 D1 staged patients. The one and two year actuarial survivals were 86% and 80% respectively although only 14 patients had been studied for more than two years at the time of the report. Importantly, the two courses of high dose cisplatinum were well tolerated although nausea and vomiting were almost inevitable accompaniments to cisplatinum administration. As yet a trial of combination MVAC given as an adjunct to local therapy has not been reported, but it is quite likely that, in this role too, MVAC toxicity will be considerable. Whether this problem of toxicity can be minimised by incorporating analogues and changing combinations while maintaining individual drug efficacy (with or without synergism) remains to be seen. This consideration is particularly important for an older, relatively unfit age group [12, 50].

While improved results with chemotherapy are heartening, the presented data require careful scrutiny and evaluation. It would appear that the natural history of invasive bladder cancer may be changed by chemotherapy. For example, brain metastases are uncommon in bladder cancer but following chemotherapy these seem to occur more frequently [2, 8, 61]. Consequently two and five year follow-ups may be less appropriate and longer periods may be necessary to compare survival data to established forms of local treatment. In addition many cytotoxic agents, especially alkylating agents are weak carcinogens and there is some evidence supporting this with cisplatinum too [15, 50].

Cytototoxic chemotherapy aside, the nature and extent of chosen forms of therapeutic intervention may have pronounced effects on patient survival. Although careful attention to grade and stage is made in most studies, tumour bulk, a most relevant factor to consider in total tumour eradication, tends to receive scant mention [25, 54]. A possible pertinent factor affecting global immunological status is blood transfusion. Blood transfusion is often given as a prelude to renal transplantation to increase graft acceptance rate and transfusions are not infrequently given in association with surgery, especially cystectomy. An association has been reported in colonic cancer between the administration of blood transfusions and the earlier development of metastases after correction for established baseline prognostic factors [4, 6]. In patients with operable breast cancer, Tartter et al. in another retrospective analysis, found that, at five years, the cummulative disease-free rate was 51% for those patients given peri-operative transfusions compared to 65% for patients who had not received blood. The two groups in this survey were comparable for age, stage, discharge, haemoglobin values, proportion of radical mastectomies and duration of follow-up [63]. Quite possibly a similar relationship exists in the case of invasive bladder cancer although not all evidence has supported these reports.

The observation that immunotherapy may have a beneficial effect on invasive bladder cancer and the development of more effective chemotherapy serve as stimuli to increase our understanding of ways in which these methods can be made more effective. This information warrants evaluation

both together and in combination with radiation therapy and surgery. These questions need to be addressed in a scientific manner by controlled clinical trials so that objective data can be obtained for optimal treatment of individual patients.

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