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Acknowledgement—This review was supported by grants from the Cancer Research Campaign.

Eur J Cancer, Vol. 27, No. 3, pp. 326–330, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Neoadjuvant and Adjuvant Therapy for Invasive Bladder Tumours

Luc Y. Dirix and Allan T. Van Oosterom

INTRODUCTION

ALTHOUGH BLADDER cancer is the fifth most common cancer in the Western world, it is only seventh in the ranking of cancer related mortality. This is due to its presentation as a superficial disease in 80–90% of new cases. Only 10% and 30%, respectively, of Tis and T1 cancers will actually develop into invasive carcinomas. The majority of patients who will eventually die of bladder cancer have muscle invasive disease at presentation. A clear distinction must therefore be made between muscle invasive and non-invasive disease, as those two entities have completely different biological behaviour, and as progression from non-invasive to invasive disease only occurs in a minority of patients [1].

The prognostic importance of muscle invasive disease is its metastatic potential [2]. At present we are hampered by the lack of reliable prognostic factors that would enable us to distinguish between local invasiveness of a tumour and its metastasing capacity. The entire group of patients with a muscle-invasive tumour has a 5-year survival rate of less than 50% regardless of the local treatment strategy applied [3]. The majority of those patients will succumb due to metastases making T2+ bladder cancer a systemic disease.

Correspondence to A.T. Van Oosterom.
The authors are at the Department of Oncology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium.
Received and accepted 29 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.

With the emergence of effective chemotherapy regimens in metastatic disease, more and more emphasis has been given to the use of cytotoxic drugs in patients with muscle-invasive disease. The current lack of other reliable prognostic factors makes the division of all N0 M0 bladder carcinomas into a superficial group and a muscle invasive group, the only distinction which is clinically useful. However, this should not lead to oversimplification. The prognosis of a small, well differentiated T2 transitional cell carcinoma is of course much better than that of an undifferentiated carcinoma with invasion into the prostate. While in the first situation one might consider chemotherapy as part of a bladder sparing strategy, in the latter it would rather be directed at treating micrometastases and/or increasing resectability, and these are very different goals.

CHEMOTHERAPY

In metastatic disease several cytotoxic agents have a single agent response rate superior to 20%. The most active drugs are cisplatin and methotrexate with both attaining a response rate in the range of 25–30%. Several other drugs such as doxorubicin, vinblastine, cyclophosphamide and 5-fluorouracil (5-FU) have a documented response rate of about 20%, making transitional cell carcinoma a relative chemosensitive tumour [4,5].

From the disease-oriented phase II trials several important conclusions can be drawn. Firstly, the anatomical location of a urothelial carcinoma has no impact on chemosensitivity, while the presence of different or mixed histology is relevant. Secondly, even in metastatic disease complete and durable remissions are possible. Thirdly, primary tumour in the bladder is very responsive to chemotherapy, as are lymph node and lung metastases, as opposed to bone and liver deposits which are less likely to respond [6,8,9].

From these studies several combinations have been derived in an attempt to further increase response rates. At present one can safely state that cisplatin and methotrexate should be present in every combination and that combination chemotherapy is superior to single agent chemotherapy with regard to the number of complete remissions. Until recently, several randomised trials comparing single agent cisplatin with combination chemotherapy failed to reveal statistically significant benefit in survival for the more toxic combinations. In a recent study, however, comparing cisplatin to methotrexate/vinblastine/doxorubicin/cyclophosphamide (M-VAC) polychemotherapy, Loehrer *et al.* [10] have demonstrated the superiority of the combination both in response rate and in survival, albeit at the cost of increased toxicity. Logothetis *et al.* [11] compared in a prospective randomised trial M-VAC to CISCA chemotherapy in patients with metastatic disease. They also found superior results both in response rate and in survival for the M-VAC combination. A trial by the EORTC Urology group compared a cisplatin and low-dose methotrexate combination to a cisplatin and intermediate-dose methotrexate and vinblastine arm. No apparent benefit was observed from the addition of vinblastine and the higher dose of methotrexate [12]. While the actual role of doxorubicin in the M-VAC combination remains controversial, possibly owing to the low dose in which it is given, the median survival of complete responders with M-VAC seems to be better than that for complete responders treated with cyclophosphamide/methotrexate/vinblastine (CMV). At present cyclophosphamide/methotrexate (CM), CMV and M-VAC are the most widely tested combinations in the neoadjuvant setting.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant cytotoxic therapy refers to the use of systemic drugs prior to a local control procedure. In principle, neoadjuvant therapy is never intended to defer the need for a radical local procedure. It has to be considered as a preliminary therapy to the local treatment. The main goal of neoadjuvant therapy is that it is given to patients with a supposed micrometastatic compartment, and that treatment of this compartment is best achieved as early as possible, i.e. prior to the removal of the primary tumour. The effects of the surgical procedure and the removal of the primary tumour are largely unknown, but it has been suggested that these could result in an accelerated growth of metastases. The potentially negative effects of surgery and/or radiotherapy on drug delivery and thus dose-intensity are such that this also favours preoperative chemotherapy. The possibility of downstaging the primary tumour and observing *in vivo* chemosensitivity, treating the micrometastases at their lowest volume and thus with a theoretically lower potential for drug resistance, are other advantages of the neoadjuvant approach. These concepts have major implications with regard to the timing and integration of these combined modality treatments. The possibility of detecting drug resistance of the primary tumour early on minimises both the exposure of patients to an ineffective treatment and the delay in the local procedure.

Several studies in the early 1980s have established the feasibility of this approach. Fagg *et al.* [13] treated 17 patients with T2-T4N0M0 disease with cisplatin 100 mg/m^2 at 3-weekly intervals. While disease progressed in 1 patient after 3 courses, in 11 a partial response was observed and median survival was significantly better for responders. The study by Raghavan *et al.* [14] confirmed these results in 50 patients with T2+ disease again with single agent cisplatin 100 mg/m^2 intravenously in 2 doses with a 3-week interval. They observed a 60% response rate including 8 patients with apparent complete response. A study by Meyers *et al.* [15] looked at the response of the bladder in patients with metastatic disease treated with CMV. They confirmed the high local response rate where 11 out of 17 achieved a clinically complete response, one of which was pathologically proven by cystectomy. Kaye *et al.* [16] used a combination of cyclophosphamide 5-fluorouracil and methotrexate in 17 patients with T3 bladder cancer. Although they only assessed response in 12 of these patients, they did not observe any major responses.

This brings us to one of the major difficulties in these neoadjuvant trials in bladder cancer, namely that in a number of cases a near complete endoscopic resection has taken place at the time of initial biopsy: these patients are thus inevaluable for response and are in effect receiving adjuvant rather than neoadjuvant therapy.

Taking all these limitations into account, it is fair to conclude from these studies that pre-emptive chemotherapy is a feasible option even in older patients [17], that a response rate including complete responses is obtainable in approximately 50–60% with single agent cisplatin [13,14,17,18], that tumour progression or metastases nearly never occur in the time period needed for 2 or 3 courses and finally that this treatment in no way seems to add to the morbidity or mortality of the local definitive treatment.

Stimulated by the higher response rates of combination chemotherapy regimens, these combinations have been tested in numerous phase II neoadjuvant studies. The largest experience has been gained with the M-VAC combination at Memorial-Sloan Kettering Cancer Center. In their latest update results are reported on 87 patients with residual muscle invasive disease

prior to M-VAC [19]. From this and other similar studies some conclusions can be made. Firstly, pathologically proven complete remissions are obtained in 20–30% of patients. The chance of achieving this is better for T2 than for T3 and is very rare in a T4 patient. Secondly, the possibility of predicting pathological CR, clinically with TUR is disappointingly low. In the M-VAC MSKCC series, 12 of 25 clinically T0 patients proved to have residual muscle-invasive disease. Thirdly, tumour downstaging is achieved in 40–60% of patients. Fourthly, non-responding patients, in spite of the fact that frank progression during treatment is very rare, fare very poorly in spite of a subsequent aggressive local approach with surgery and/or radiotherapy. This means that response to chemotherapy is in itself of major prognostic significance, and this does not necessarily imply a cause-effect relationship. In current protocols, the initial response is being used as a guideline for further treatment. Fifthly, non-transitional cell carcinomas do poorly on these combinations and *in situ* carcinoma is also considered to be chemoresistant. It is also clear from these studies that neoadjuvant chemotherapy is not preventive for the subsequent evolution of Tis into invasive carcinoma. This is of course of major importance for patients treated with a partial cystectomy or in whom bladder preservation is considered. Sixthly, while a pathological CR is obtainable in a significant proportion of T2 and T3a patients, bladder preservation remains very controversial due to the clinical staging inaccuracy and the risk of extravesical tumour growth.

At present two trials with neoadjuvant chemotherapy for invasive bladder cancer have been completed. In the first one by Shearer *et al.* [20], 376 patients were randomised in a prospective trial using neoadjuvant and maintenance methotrexate. No survival benefit was observed. In two parallel studies in Australia and England, single agent cisplatin was used followed by radical radiotherapy. Because of problems with patient accrual, those trials closed prematurely and separate and meta-analysis have failed to show any clinically relevant benefit [21].

In order to define the role of neoadjuvant chemotherapy more clearly, two large cooperative trials have been initiated. The MRC–EORTC randomised controlled trial will test the influence of three pre-emptive cycles of CMV followed by radiotherapy or cystectomy on survival. The Intergroup study will investigate the use of M-VAC and cystectomy versus cystectomy.

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy is given following the completion of local treatment. This treatment option has been shown to increase survival in patients with osteosarcoma and in premenopausal patients with stage II breast carcinoma [22]. It has recently been shown to be effective in stage C colon carcinoma [23]. As with neoadjuvant chemotherapy, the actual goal remains the same, i.e. the treatment of a potentially present micrometastatic compartment. The major advantage of adjuvant therapy is the available pathological staging. Our knowledge of clinical staging inaccuracy in general, and more specifically in bladder cancer, underscores the importance of rigid pathological criteria, such as nodal involvement, muscular invasion and extravesical growth. This approach will certainly lead to better patient selection and thus will minimise the unnecessary exposure of patients to toxic drugs. The fact that local treatment has been completed eliminates a potentially dangerous time delay associated with the neoadjuvant chemotherapy. It also eliminates the risk of refusal of patients to undergo local treatment, once neoadjuvant chemotherapy has obtained a clinically complete response.

Adjuvant chemotherapy has also major disadvantages, foremost of these being the loss of *in vivo* chemosensitivity testing, with the associated loss of the prognostic value associated with this response. This implies that ineffective therapies will be given to patients without any possibility of assessment. The question of the necessary number of courses has also to be dealt with in a pragmatic fashion, because it is impossible to assess clinical benefit in an individual patient. Another important argument against adjuvant chemotherapy comes forward in most trials using this approach. Patient acceptance of chemotherapy seems to be much lower for adjuvant than for neoadjuvant chemotherapy, leading to a form of patient selection. Finally, timing and dosing of adjuvant chemotherapy after surgery is of major importance, especially as there are arguments of an accelerated growth phase of the micrometastatic compartment.

In 1988, Logothetis *et al.* [24] reported the MD Anderson results of adjuvant CISCA chemotherapy given in a non-randomised trial. Out of 339 patients who underwent cystectomy, 206 were considered to have low risk disease as opposed to the remaining 133 having a high risk for the development of local recurrence and metastases. High risk was defined as the presence of vascular or lymphatic invasion, extravesical growth, lymph node involvement or extention into the pelvic viscera. Out of the 133 high risk patients, 62 either refused treatment or were considered medically unfit to receive the intended 5 cycles of CISCA, leaving only 71 patients receiving chemotherapy. The 5-year survival for the low risk group was 76% versus 70% of the high risk group receiving chemotherapy and 37% for the untreated high risk group. The results of this trial are very encouraging, but it remains a non-randomised, selective comparison based on compliance and the general condition of patients. The comparable 5-year survival figures of the treated high risk group and the low risk group are strong evidence in favour of adjuvant treatment. However, one should consider the fact that the "high risk" group is also a "low risk" group with regard to general condition, something that in itself would contribute to better survival of this group.

In a randomised trial, the National Bladder Cancer Group studied the potential benefit of single agent cisplatin after combined radiotherapy and surgery. Only 9 out of 43 patients (21%) completed the protocol, and it is not surprising that no benefit was observed in the cisplatin treated group (25). In another randomised trial with preoperative radiotherapy versus no radiotherapy, followed by surgery and a second randomisation to 5-FU or no 5-FU, patient compliance was again very poor and no clear benefit was observed. One has to realise that 5-FU is also not the drug of choice in this situation.

In the study of Richards *et al.* [26] 100 patients clinically staged T3, NX, M0 bladder cancer were randomised to receive at least 4 courses of adjuvant doxorubicin and 5-fluorouracil at 3 weekly intervals. Treatment with chemotherapy started within three months of the start of radical radiotherapy. The 3-year and 5-year survival figures are not significantly different. Here again the selected drug combination and its timing are suboptimal.

In the study by Skinner *et al.* [27], 91 patients were randomised to receive 4 courses at 4 week intervals of cisplatin 100 mg/m^2, doxorubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2. Out of 229 patients with pT3, pT4 or N+ and M0 disease, 49 patients were excluded because of age (> 75 years), prior malignancy or general medical factors. Of the remaining

160, 101 patients agreed to participate in this trial, but 10 were excluded for reasons of histology, leaving 91 patients at randomisation. 11 of the 44 patients randomised to the chemotherapy arm elected not to be treated and only 21 out of 44 patients completed the four cycles as planned. At three years the probability of disease recurrence was 30% in the chemotherapy arm versus 54%; the chance of dying of bladder cancer within 3 years was 34% versus 50% in favour of the chemotherapy arm. Median survival time for patients in the chemotherapy group was 4.3 years compared to 2.4 years in the observation group. However at the 48% survival level the two lines in fact cross and survival of the control group thereafter is superior. This trial, however encouraging its results superficially may look, cannot be considered conclusive as patient numbers and thus statistical power are too small.

At present it must be concluded that it is impossible to make a definitive judgement on the role of adjuvant chemotherapy. Additional studies with adequate numbers of patients using the most active drugs are needed.

RADIOTHERAPY

Radical radiotherapy offers the possibility of a definitive local treatment of bladder cancer without loss of bladder function. It is successful in Ta and T1 tumours. The 5-year survival figures of patients with muscle invasive bladder cancer treated with radical radiotherapy are dependent on several prognostic factors such as absence of ureteral obstruction, near complete transurethral resection, low tumour grade, a papillary versus a sessile tumour growth and clinical stage. Tumour sterilisation is very uncommon in the T3 and T4 G2-3 patients despite high doses of 60 to 70 Gy [1].

It has generally been felt that when combined radiation and surgical treatment are being planned, preoperative irradiation is the optimal association, although no direct comparative studies using other permutations have been performed. Two randomised trials compared preoperative irradiation and cystectomy versus radical cystectomy. In the smaller Houston trial [28] with 67 patients, a better survival was reported for patients receiving the combined treatment. The larger London trial reporting on 189 patients compared pre-operative pelvic radiotherapy (40 Gy) and elective radical cystectomy versus radical radiotherapy (60 Gy). In patients not achieving CR after radical radiotherapy, salvage cystectomy was feasible with an acceptable morbidity. No clear advantage was observed for the combined approach [29]. Nevertheless it is still widely accepted in many centres that at present optimal local treatment for patients with muscle-invasive bladder cancer is surgery, while older and more fragile patients are best treated with radiotherapy. Although the overall view from those studies which have addressed the role of preoperative radiotherapy is that there is no clear benefit in survival, in most studies improved local control was observed. It must be remembered that most of these trials were performed in the 1970s, since when marked improvements have been made in treatment planning and radiotherapy equipment.

Combined treatment with radiotherapy and cisplatin was given to 70 patients with stage T2+ bladder cancer, considered unsuitable for surgery [30]. A complete response rate of 70% was obtained and at four years overall survival for stage T2 was 64%. Several studies, including phase II studies are currently being completed in order to evaluate combined cisplatin and radiation treatment [31]. A similar approach has been tested at the Massachusetts General Hospital using CMV chemotherapy upfront following maximal transurethral resection [32]. After 2 CMV cycles, 40 Gy was given to the pelvis with concomitant cycles of cisplatin. After cystoscopic reevaluation, complete responders were treated with irradiation up to 66 Gy, incomplete responders underwent salvage cystectomy. Among the 42 patients who completed the protocol, 82% were alive in the chemotherapy plus radiotherapy arm versus 38% in the salvage cystectomy arm. Because of the high local response rate, a randomised phase III trial is now testing this chemotherapy plus radiotherapy association and the final results have to be awaited.

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Eur J Cancer, Vol. 27. No. 3, pp. 330–333, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Optimal Management of Superficial Bladder Cancer

J.A. Witjes and F.M.J. Debruyne

INTRODUCTION

OPTIMAL MANAGEMENT of superficial bladder cancer is based on a knowledge of epidemiology, presenting symptoms and natural course.

Bladder cancer is, after prostatic cancer, the most frequent urological cancer. It is 3–4 times more frequent in men. As in all epithelial tumours, the incidence rises with age, with the highest incidence in the sixth and seventh decade. Several risk factors have been identified, of which smoking is the most important. More than 90% of bladder tumours are of the transitional cell type. Less than 10% of the tumours are adenocarcinomas and squamous cell carcinomas.

The key symptom is haematuria, whether macroscopic or microscopic. This should always raise suspicion of the diagnosis of a malignancy, until proven otherwise. In the diagnostic work, history (irritative bladder symptoms, recurrent infections) and physical examination should be followed by urine investigations, especially urine cytology. Together with intravenous urography (IVU) and urethrocystoscopy (UCS) the initial diagnosis of a (superficial) bladder cancer can be made.

The treatment of choice is an adequate transurethral resection of the tumour (TURT) together with random biopsies from the bladder and the prostatic urethra, unless there are major contraindications for surgery and/or anaesthesia. Together with a bimanual examination before and after operation the tumour category and grading can be assessed [1]. In case of contraindications against the TURT, initial therapy could be intravesical instillations of chemotherapeutic or immunotherapeutic agents, which are discussed below. If there is any doubt as to whether the initial TURT has been complete, a new UCS with TURT has to be planned after 4–6 weeks.

Further treatment depends on the pathological classification in which two major categories can be identified. Approximately 75% of the primary bladder tumours are superficial, invading as far as the lamina propria, and not infiltrating the muscle of the bladder wall (pTa, pT1, pTis). The other group of tumours are the muscle infiltrating bladder tumours (pT2-pT4b).

In the case of an infiltrating transitional cell carcinoma (TCC) further investigations to determine the presence or absence of

Correspondence to J.A. Witjes.
The authors are at the Department of Urology, University Hospital, P.O. Box 6500, Nijmegen, The Netherlands.
Received 10 Dec. 1990: accepted 12 Dec. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.