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Multimodal Treatment of Locally Advanced Transitional Cell Bladder Carcinoma in Elderly Patients

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22 patients with locally advanced (T3–T4, M0) transitional cell bladder carcinoma, age greater than 70 years, with medical contraindication or refusal of radical cystectomy, were treated following an ample transurethral resection (TUR), with three chemotherapy cycles. Each cycle consisted of 5-fluorouracil 500 mg/m² intravenously (i.v.) on days 1 and 8, epirubicin 60 mg/m² i.v. on day 1 and cisplatin 50 mg/m² i.v. on day 1. Cycles were repeated every 3 weeks. Subsequently, patients were submitted to a repeat TUR on the area of the initial neoplasm. At computed tomography (CT) scan evaluation, response rate to chemotherapy was 54.5%, with two complete responses. No residual disease (R0) at postchemotherapy TUR was encountered in 8 cases (36%), and microscopic disease (R1) in 4 cases (18%). Median duration of complete responses (R0) was 13.5 months (range 7–57+). Radiation therapy was carried out in 12/14 patients with residual disease at repeat TUR. Overall median duration of response was 10.2 months, while overall actuarial median survival was 11.6 months. Four-year survival was 29%. The approach described was feasible. The chemotherapy regimen employed was not as active as current regimens used in younger patients. The search for more active regimens which are tolerable by the elderly is important.

Key words: bladder cancer, elderly patients, chemotherapy
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INTRODUCTION

BLADDER CANCER represents an important cause of morbidity and mortality in the elderly, due to its more frequent occurrence with increasing age, to its severity in terms of symptoms and survival, and to the physical and psychological sequelae of curative treatments.

In particular, radical surgery may be not feasible due to the general conditions of these often frail patients or to specific anaesthesiological contraindications. Radiotherapy is not as effective as surgery in controlling the primary disease [1], and its toxicity may be particularly considerable in elderly patients. Finally, chemotherapy with intensive regimens, such as the M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) or the CMV (cisplatin, methotrexate, vinblastine), is often not applicable to this population of patients [2].

Ample transurethral resection (TUR) associated with chemotherapy is feasible in patients with invasive bladder cancer, and can have a curative potential in selected cases [3].

In a previous study, a four-drug regimen was able to induce an 80% response rate with acceptable toxicity in locally advanced bladder cancer [4].

Following that experience, the chemotherapy schedule previously evaluated was modified in order to make its administration feasible in a population of elderly patients. This modified regimen was integrated with TUR and radiotherapy in a consecutive series of elderly patients with locally advanced bladder carcinoma not amenable to radical cystectomy.

The results obtained are the subject of the present report.

PATIENTS AND METHODS

From February 1988 to May 1992, all consecutive eligible elderly patients with locally advanced bladder cancer were entered into the study. Conditions of eligibility included histological diagnosis of transitional cell bladder carcinoma, locally advanced disease (T3–T4, M0), age greater than 70 years, performance status (PS) greater than 60, life expectancy greater than 3 months, renal, hepatic and cardiac functions adequate to the chemotherapy programme, no previous systemic chemotherapy or radiotherapy and no other malignancies. Radical cystectomy was either medically contraindicated or refused in all patients. Patients deemed to be operable were not included in this study. Staging procedures included clinical examination, abdominal and pelvic computed tomography (CT) scans, chest X-rays, blood chemistry, cystoscopy and wide TUR aimed at complete removal of the tumour. Patients who only had a tumour biopsy were not entered into the study. The stages of disease are defined according to the TNM classification [5].

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After the initial wide TUR, subsequent treatment consisted of three chemotherapy cycles. Each cycle consisted of 5-fluorouracil 500 mg/m^2 intravenous (i.v.) on days 1 and 8, epirubicin 60 mg/m^2 i.v. on day 1 and cisplatin 50 mg/m^2 i.v. on day 1. Cycles were repeated every 3 weeks. In case of obstructive renal impairment at presentation, carboplatin 200–250 mg/m^2 i.v. was given instead of cisplatin. Following three chemotherapy cycles, patients were clinically restaged with CT scans and repeat TUR on the area of the initial neoplasm. The absence or presence of residual tumour was defined according to the TMN classification [5]. In case of no residual disease (R0), no further treatment was given, while patients with either microscopic (R1) or gross (R2) residual disease received radiotherapy to the bladder (50–60 Gy in 25–30 sessions).

Toxicity of treatment and response were scored according to the WHO criteria [6]. Survival curves were defined according to the product-limit method [7]; differences between subgroups were assessed by means of the log-rank test [8].

In the study period, 22 patients entered into the study. 15 patients were male, seven were female; median age was 74 years (range 70–84), median PS was 80 (range 60–100). Reasons for non-operability included chronic obstructive pulmonary disease in 5 patients, diabetes in 2 patients and peripheral vasculopathy in 3 patients. 8 patients who were older than 75 years, were not considered fit for operation, and 4 declined radical cystectomy.

T and N classification was as follows: T3a in 5 patients, T3b in 13, T4 in 4, N0 in 19 and N2 in 3 patients. Histological grading included G2 in 3 patients, G3 in 18, GX in 1 patient.

5 patients received carboplatin instead of cisplatin because of decreased renal function (serum creatinine from 1.5 to 2.5 mg/dl).

RESULTS

Clinical complete remission (CR) to chemotherapy was noted in 2 patients, partial remission (PR) in 10, stable disease (SD) in 6 and progressive disease (PD) in 4. The overall response rate (CR + PR) was 54.5%. R0 at postchemotherapy TUR performed in all patients was encountered in 8 cases (36%), whereas downstaging (R1) was obtained in 4 patients. The correlation between radiological (repeat CT scan) and endoscopic response (repeat TUR) is shown in Table 1. The median duration of complete responses (R0) was 13.5 months (range 7–57+), with 2 patients alive without recurrence at 33 and 57 months, respectively, and 1 patient dead without disease at 52 months. Local recurrence in these 8 R0 patients was superficial only in 1 patient, infiltrating in 4 patients. One of the latter 4 patients also presented distant metastases.

Toxic effects of chemotherapy are reported in Table 2. No toxic deaths occurred. Median relative dose intensity of drugs was 96% (range 27–100) for cisplatin, 90% (range 82–100) for epirubicin, 89% (range 59–100) for 5-fluorouracil and 75% (range 42–82) for carboplatin.

Radiation therapy was carried out in 12/14 patients with residual disease at control TUR. 3 of 8 evaluable patients responded. No patient achieved a pathological CR with radiation therapy. Radical cystectomy was eventually performed in 1 patient for recurrent disease after chemotherapy and TUR, and in another for recurrent disease after radiotherapy. Explorative laparotomy was only performed in 1 additional patient with progressive disease after radiotherapy.

Overall median duration of response was 10.2 months, while overall actuarial median survival was 11.6 months (Figure 1). A good PS (< 80 versus ≥ 80) and clinical response (R0 versus R1 + R2) were significantly ($P < 0.05$) associated with a longer survival at univariate analysis.

Table 1. Correlation between radiological response and residual disease at TUR

Radiological response (CT scan)	Residual disease (repeat TUR)	Progression-free interval in R0 (months)
CR = 2 PR = 3 SD = 2 PD = 1	R0 = 8	52, 33+ 16, 11, 57+ 8, 15 7
CR = 0 PR = 3 SD = 1 PD = 0	R1 = 4	
CR = 0 PR = 4 SD = 3 PD = 3	R2 = 10	

CT, computed tomography; TUR, transurethral resection; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 2. Toxicity of chemotherapy

	G1	G2	G3	G4
Bone marrow	5	6	1	1
Renal	4	—	—	—
Hair	1	6	6	—
Gastrointestinal	4	6	3	3
Cardiac	1	—	—	1
Infection	3	1	1	—
Oral	1	1	—	—

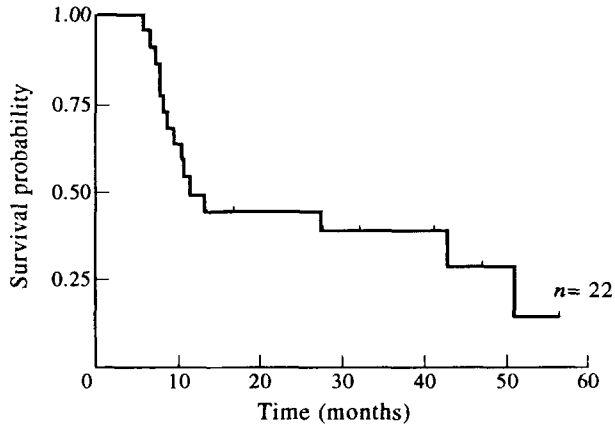

Figure 1. Overall survival.

DISCUSSION

In our previous experience [4], a four-drug regimen including cisplatin, doxorubicin, fluorouracil and teniposide yielded an 80% response rate (26% complete response rate) in locally

advanced bladder cancer, with 5/19 evaluable cases found to be histologically tumour-free at cystectomy. It was felt that this regimen was probably not intensive enough for young patients, but further evaluation in elderly patients seemed warranted. However, the occurrence of three cardiac deaths was of concern. The chemotherapy regimen evaluated in this study differs from the one previously reported [4] as presurgical treatment in two respects: (1) replacement of doxorubicin by epirubicin, an anthracycline derivative with similar activity and less cardiotoxicity than the parent compound [9], and (2) deletion of teniposide, whose activity as a single agent is not established. As regards response, the new regimen was less active in terms of response rate (57 versus 80%) and CR rate (9 versus 20%), while the rate of histologically negative results (36 versus 26%) is not comparable due to the different means of assessment in the two studies (TUR versus radical cystectomy). Toxicity and relative dose intensity were comparable.

In the last few years, the chemotherapeutic management of these patients has oscillated between an attempt to offer them aggressive treatments originally devised for non-elderly patients, often with compromises on their intensity, and a tendency to develop specific treatment modalities for these patients.

Within the former group is the experience developed at the M.D. Anderson Cancer Center in 38 elderly (> 75 years) patients collected in a 10-year period, and treated with aggressive chemotherapy programmes [10]. Although cisplatin-containing regimens could be safely administered to this population of elderly patients, selection factors should be taken into account, as indicated by the small number of patients treated over a long period at a major cancer center.

Alternatively, some reports have dealt with specifically devised regimens for these patients. Arena and colleagues [11] evaluated a combination of carboplatin and 5-fluorouracil in poor performance patients (median age 67 years) with advanced urothelial cancer. Results were not particularly encouraging, with a 20% response rate and only one complete remission in 20 evaluable patients. Instead, Waxman and colleagues [12] treated 33 evaluable patients, without exclusion on the basis of age, with a combination of methotrexate, vinblastine, mitoxantrone and carboplatin, reporting a 63% response rate with a 27% complete response rate. Also, Stalder and colleagues [13] reported encouraging results (44% response rate with one complete remission in 18 evaluable patients) with a combination of carboplatin and methotrexate used in patients with impaired renal function (median age 64 years). The association of methotrexate and a platinum analogue is probably of importance in the management of elderly patients, as it is when younger patients are treated.

In this study, the duration of CRs was encouraging, with a median of 16 months, while overall survival was not, with a median of less than 1 year. This fact reflects the very poor prognosis of patients not responding to chemotherapy and submitted to radiation therapy (the median survival of those 12 patients was only 8 months). In fact, after a sharp decline in the first months, the survival curve tends to plateau with a 29% 4-year survival (all eligible patients), suggesting a beneficial effect of treatment in a minority of patients. Intuitively, this appears to support the importance of achieving a response in the early phases of treatment. From another point of view, it can be that response to chemotherapy only reveals a state of chemosensitivity, which might be an independent prognostic factor *per se*. The potential curative effect of the initial TUR at least in some T3 patients should be taken into account.

In a large series, radiation therapy yielded a 5-year survival rate of approximately 10–20% in T3–T4 tumours [14].

If our results are compared to a comparable series of patients treated with cisplatin and radiation therapy by the National Bladder Cancer Group [15], median survival for T3–T4 patients appears to be shorter (11 versus 18 months), although the greater median age (76 versus 70 years) in our series should be taken into account. The 3-year survival was of the same order of 30–40%.

In conclusion, it appears from our data that a chemotherapy–TUR approach with radiotherapy as salvage treatment is feasible in elderly patients with locally advanced bladder carcinoma. However, no survival benefit is apparent as compared to radiotherapy alone or combined with chemotherapy. The chemotherapy regimen employed was not as active as current regimens used in younger patients, and, as obtaining a response to chemotherapy appears to be an important determinant for survival, the search for more active regimens which are tolerable by the elderly is important.

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