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Mitomycin C treatment of advanced, hormone-resistant prostatic carcinoma: a phase II study

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Summary. From February 1984 to February 1987, 29 patients with advanced, hormone-resistant prostatic carcinoma were treated with mitomycin-C at a dose of 20 mg/m^2 every 6 weeks (15 mg/m^2 in patients >75 years old and in those who had undergone previous radiotherapy). In the 27 evaluable patients, there were no complete remissions (CR), 2 partial remissions (PR), 14 stabilizations (STAB), and 11 cases of progressive disease (PRO). Ten stabilized patients showed significant pain reduction. Toxicity was minimal. The actuarial median survival was 10.8 months. In this study, mitomycin C was not active in terms of CR + PR; however, a beneficial symptomatic effect was frequently observed.

Introduction

Mitomycin C (MMC) has demonstrated activity against a spectrum of tumors, including adenocarcinomas originating in the breast, gastrointestinal tract, and lung [2]. MMC was recently incorporated in combination chemotherapy regimens for advanced prostatic carcinoma [4]; however, its activity as a single agent is as yet ill-defined. A phase II study was started at our institute in 1984 to assess the efficacy and toxicity of MMC in prostatic carcinoma.

Patients and methods

From February 1984 to February 1987 all consecutive, eligible patients seen at our institute were enrolled in the study. Conditions of eligibility included histological proof of prostatic adenocarcinoma, stage-D2, hormone-resistant disease (defined as progressive, symptomatic disease after orchiectomy or during treatment with the LHRH analogue, Buserelin, or antiandrogens), white blood cell count (WBC) >4,000/mm, platelet (PLT) count >120,000/mm^3, serum creatinine <1.4 mg/dl, absence of chronic lung disease and of cardiac failure or clinically relevant arrythmia, and a Karnofky performance status (PS) >40. Provided that all conditions of eligibility were met, age limit was set no upper.

MMC was given as an i.v. push at a dose of 20 mg/m^2 every 6 weeks. In patients older than 75 years or previously treated with radiotherapy, the dose was decreased to 15 mg/m^2. WBC, PLT, and acid phosphatase determinations were carried out before each MMC cycle. In cases of leukothrombocytopenia, treatment was delayed until bone marrow recovery.

Examinations necessary to define response were repeated every 2–3 cycles. A minimum of two cycles were required to define response unless obvious progression occurred after the first cycle. The National Prostatic Cancer Project (NPCP) criteria [6] were used for definition of response, which was classified as complete response (CR), partial response (PR), stabilization (STAB), and progressive disease (PRO). Toxicity was scored according to the WHO criteria [5]. Actuarial survival was calculated according to the life-table method [1].

Results

A total of 29 patients were entered in the study; their characteristics are shown in Table 1. In all, 82 MMC cycles were given (median, 3; range, 1–6). Two patients were unevaluable (early death due to progressive disease in one, loss to follow-up in one). In the 27 evaluable patients,

Table 1. Patient characteristics and response

Number of patients	29
Median age (range)	68 (53–84)
Median PS (range)	70 (50–100)
Site of metastatic disease	
Bones	27
Lung	1
Lymph nodes	7
Measurable/evaluable disease	7/22
Previous hormonal treatment	
Orchiectomy (± antiandrogens)	23
Buserelin	4
Cyproterone acetate	2
Median time since orchiectomy (years)	2
Response	
Unevaluable	2
CR	0
PR	2
STAB	14
PRO	11
Actuarial median survival in months (all eligible patients)	10.8

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Table 2. Toxicity

	Grade				
	0	1	2	3	4
Bone marrow	19	4	3	1	0
Nausea and vomiting	24	0	3	0	0

there were no CRs, 2 PRs, 14 STABs, and 11 PROs, for a 59% NPCP response rate (responding/evaluable patients). If the responding/eligible patient ratio is considered, the NPCP response rate was 55%. Ten patients in the STAB category showed significant, clinically appreciable pain reduction and PS improvement. The median duration of response (PR + STAB) was 20 weeks. Toxicity was tolerable, as reported in Table 2, and most patients had no toxic signs at all. None of the patients manifested cardiac, renal, or pulmonary toxicity. The actuarial median survival (all 29 eligible patients) was 10.8 months, as shown in Fig. 1.

Discussion

Although prostatic carcinoma is a common disease, relatively few patients can undergo chemotherapy, due to old age and poor general condition. Furthermore, few patients have measurable lesions, and the interpretation of response in patients with evaluable disease may be difficult. Moreover, the significance of the STAB category in the NPCP criteria is uncertain, although it is likely that it represents an indication of response to therapy [7]. The role of chemotherapy in patients with advanced prostatic carcinoma has recently been reviewed, and little evidence has been found of a beneficial effect [8].

In this study the efficacy of MMC was investigated. The "true" response rate was low, but the majority of patients remained stable, often experiencing a noteworthy symptomatic benefit. However, the final impact of MMC on the course of the disease remains uncertain; in this study survival was representative of that generally reported in such patients [8].

The EORTC Genitourinay Group evaluated the activity of MMC against prostate cancer in a phase II study. The drug was given at a dose of 15 mg/m^2 every 6 weeks. In a preliminary analysis [3], a 21% PR rate was reported, with 58% of the patients remaining STAB; the median time to PRO was 7 months. Side effects were slight. These results and those of the present study indicate that at the dose given MMC is well tolerated and has some activity against prostate cancer. More extensive studies are needed to determine whether MMC is superior to other chemotherapeutic agents, or even to no treatment at all.

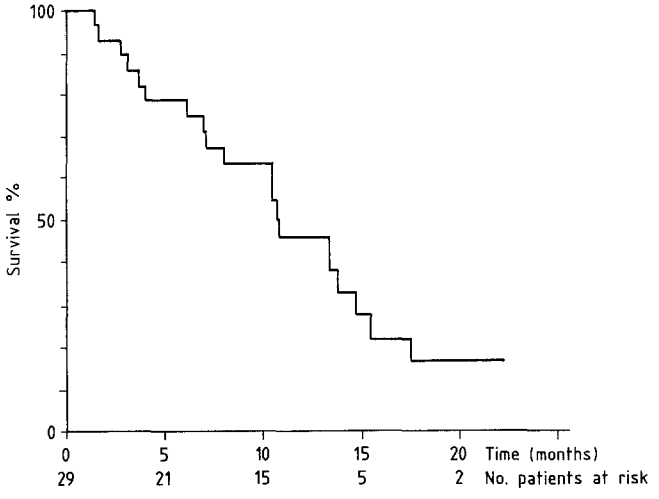

Fig. 1. Overall survival

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