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CLINICAL INVESTIGATION **Bladder**

ACCELERATED RADIOTHERAPY, CARBOGEN, AND NICOTINAMIDE (ARCON) IN THE TREATMENT OF ADVANCED BLADDER CANCER: MATURE RESULTS OF A PHASE II NONRANDOMIZED STUDY

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Purpose: We previously showed that accelerated radiotherapy combined with carbogen and nicotinamide (ARCON) was an effective approach to use in the radical treatment of patients with advanced bladder carcinoma. Interim analysis from this Phase II study showed that it achieved a high level of locoregional control and overall survival (OS) and an acceptable level of adverse events.

Methods and Materials: From 1994 to 2000, a total of 105 consecutive patients with high-grade superficial or muscle-invasive bladder carcinoma were given accelerated radiotherapy (50–55 Gy in 4 weeks) with carbogen alone or ARCON. End points of the study were OS, disease-specific, and local regional relapse–free survival, and for late adverse events, urinary (altered urination frequency, incontinence, hematuria, and urgency) and bowel dysfunction (stool frequency and blood loss).

Results: At 5 and 10 years, local regional relapse–free survival rates were 44% after ARCON excluding the effect of salvage treatment and 62% after ARCON including the effect of salvage treatment ($p = 0.04$). Five- and 10-year rates were 35% and 27% for OS and 47% and 46% for disease-specific survival. The highest actuarial rate for Grade 3 or worse late urinary or bowel dysfunction was observed for altered urinary frequency (44% of patients had urinary events every 1 hour or less) and stool frequency of four or more events (26% at 5 years).

Conclusions: Historic comparisons with other studies indicate no evidence of an increase in severe or worse adverse events and good permanent control of bladder disease after ARCON radiotherapy. © 2009 Elsevier Inc.

Bladder carcinoma, ARCON, Late adverse events, Disease-specific survival, Relapse-free survival.

INTRODUCTION

The optimal treatment for patients with muscle-invasive bladder cancer is uncertain (1, 2). Although radical cystectomy is still considered by many to be the gold-standard treatment, there is strong evidence to support the use of radical radiotherapy (RT) as an alternative (1). Clinical nonrandomized comparisons indicate that despite clear case selection for younger patients with better performance status in surgical cohorts, radical RT produces rates of disease control and survival equivalent to whole-bladder surgical ablation (for reviews see [1–4]). A policy of initial radical RT with salvage cystectomy reserved for patients with residual disease or local recurrence has the advantage of possible organ preservation (1, 5) and a rate of survival similar to that of cystectomy (6–8). The disadvantage of this approach is the need for continued surveillance and an ongoing risk of developing additional transitional carcinoma in the bladder and elsewhere in the urothelial tract.

Despite the many clinical studies undertaken to date, 5-year disease-free survival and overall survival (OS) rates for patients with muscle-invasive bladder cancer are low, with only a modest increase in survival reported since the mid-1980s (for review of studies, see [4, 9]). One possible limitation to the success of RT in eradicating clonogenic tumor cells is the enhanced radiation resistance of hypoxic tumor cells (10). Immunohistochemical studies using such putative markers of cellular hypoxia as carbonic anhydrase IX and glucose transporter-I protein have confirmed a median hypoxic fraction of 10% in a range of transitional cell bladder carcinomas (11). Furthermore, inferior survival was seen in patients with high levels of glucose transporter-I protein, carbonic anhydrase IX, vascular endothelial growth factor, and hypoxia inducible factor 1 expression (11, 12).

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There have been various attempts to modify hypoxia in radical RT trials for patients with bladder cancer by using hyperbaric oxygen and misonidazole, an oxygen mimetic chemical radiosensitizer (13–15); for a comprehensive review, see (4). A more recent approach is a schedule of accelerated RT to overcome tumor cell proliferation, carbogen to overcome diffusion-limited hypoxia, and nicotinamide to minimize capillary bed shutdown and thereby reduce perfusion-related acute hypoxia. This multimodality approach, known as ARCON, was proposed more than a decade ago (16), and against a background of successful Phase II studies (17–20), has been evaluated in two Phase III randomized trials of patients with head-and-neck cancer and patients with bladder cancer. The studies have only recently been closed to accrual.

This report presents mature results of a pilot study (median follow-up, 102 months in survivors) of patients with advanced bladder cancer treated with an ARCON schedule of 50–55 Gy in 4 weeks plus carbogen and nicotinamide or carbogen alone given with each RT treatment. The analysis focuses on both the tumor end points of locoregional relapse–free survival (LRRFS), disease-specific survival (DSS), and OS and on long-term adverse events affecting bladder and bowel function.

METHODS AND MATERIALS

Between April 1994 and Dec 2000, a total of 105 patients with high-grade superficial (T1, G3) or muscle-invasive (T2, T3A, or T3B) transitional cell carcinoma of the bladder were sequentially entered into a Phase II prospective program to evaluate ARCON in patients with bladder cancer. The study was approved by the local research ethics committee, and all patients gave informed written consent. Staging investigations including chest x-ray and abdomino-pelvic computed tomography scan to exclude metastatic disease.

Demographic and RT details have been published previously (17). Briefly, median age was 74 years (range, 38–87 years), with 93 men and 12 women. Tumor stage was T1 in 9 patients, T2 in 35 patients, T3 in 60 patients, and T4 in 1 patient. Staging is based on the International Union Against Cancer staging system in use at the time of patient entry (21). Five patients had Grade 1 disease, 26 had Grade 2 disease, and the remainder had Grade 3 disease. All patients with T1 tumors had Grade 3 histologic characteristics. The RT was delivered using a computed tomography–planned volume and a nonconformal three- or four-field plan. The first 16 patients received a dose of 50 Gy in 20 daily fractions in an overall treatment period of 4 weeks, and the remainder received 55 Gy in 20 fractions in 4 weeks prescribed to the intersection point. All patients received the full course of RT.

Carbogen (95–98% oxygen, 2–5% carbon dioxide) breathing was started 5 minutes before RT and continued throughout radiation delivery. In addition, nicotinamide was administered orally 1½ hours before radiation. The initial dose used was 80 mg/kg, which was decreased to 60 mg/kg after encountering troublesome toxicity, and in 4 patients, a dose of only 40 mg/kg was given. Forty-six patients received ARCON, and 59 received RT and carbogen. Nine of these patients had been scheduled to receive ARCON, but were found to have a contraindication to nicotinamide. This included coexisting vascular disease or coadministration of angiotensin-converting enzyme inhibitor.

Patients were seen before treatment, weekly during RT, and thereafter on Weeks 6 and 8 after the start of treatment. At each visit, bowel and urinary functions scores based on the Dische scoring system were collected (22). Late adverse events were scored using the same scoring system at 3, 6, 9, and 12 months and thereafter 6 monthly to 5 years from treatment, followed by annual assessments.

Tumor control was based on cystoscopic examination at 6 months after RT and 6 monthly thereafter for a total of 5 years or more, depending on the success of tumor control. Patients were considered for salvage cystectomy where muscle-invasive recurrence was documented.

The OS, DSS, LRRFS, and late adverse event actuarial rates were calculated using the Kaplan-Meier method. Comparisons between curves were made using log-rank test. All patients were considered to have locoregional control if there was complete absence of tumor 6 months or more after RT, as defined on cystoscopy. Those who did not achieve complete remission at 6 months were defined as never disease free. The OS was defined from the first RT treatment to death. The DSS was defined from the first RT treatment to death from locoregional or distant disease.

RESULTS

The LRRF, DSS, and OS actuarial time-incidence curves are shown in Fig. 1. Because survival estimates for patients

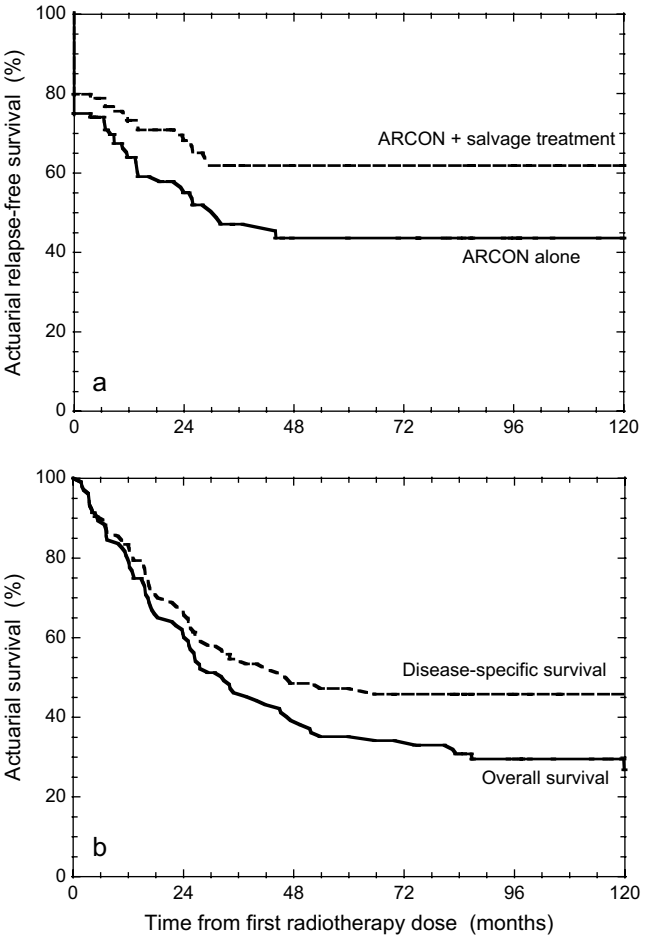

Fig. 1. (a) Actuarial incidence curves for relapse-free survival after accelerated radiotherapy, carbogen, and nicotinamide (ARCON; solid line) or after ARCON combined with salvage treatment for tumor recurrence or residual disease (dashed line). Log rank $p = 0.04$. (b) Overall survival (solid line) and disease-specific survival (dashed line).