Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 4, pp. 990–998, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.02.008

CLINICAL INVESTIGATION **Prostate**

HEMOGLOBIN LEVELS DO NOT PREDICT BIOCHEMICAL OUTCOME FOR LOCALIZED PROSTATE CANCER TREATED WITH NEOADJUVANT ANDROGEN-SUPPRESSION THERAPY AND EXTERNAL-BEAM RADIOTHERAPY

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Purpose: To investigate whether hemoglobin (Hb) levels affect outcome in men with localized prostate adenocarcinoma (LPA) treated with neoadjuvant androgen-suppression therapy (NAST) and external-beam radiotherapy (EBRT).

Methods and Materials: A total of 563 men with LPA treated with NAST (median: 5.3 months) and EBRT who had Hb levels during treatment were retrospectively reviewed. Patient, tumor, and treatment variables, including the following Hb variables, were subjected to univariate and multivariable analyses to identify factors that predict biochemical control (bNED) and overall survival (OS): pre-EBRT Hb, Hb nadir during EBRT, and change in Hb from pre-EBRT to nadir during EBRT.

Results: Median PSA follow-up was 4.25 years. Forty-nine percent of men were anemic during EBRT, with a median Hb of 13.4 g/dL, and 68% experienced a decline in Hb from pre-EBRT to during EBRT of median 0.6 g/dL. Five-year Nadir + 2 bNED and OS rates were similar for anemic and nonanemic patients during EBRT. High percent-positive biopsies, PSA and Gleason score, and use of AA monotherapy predicted worse bNED. High stage and age predicted worse OS. Hb variables were not predictive of bNED or OS.

Conclusions: Anemia is a common side effect of NAST and is usually mild. Hb levels, however, do not predict biochemical control or survival.

Hemoglobin, Androgen-suppression therapy, External-beam radiotherapy, Prostate cancer, Prostate-specific antigen.

INTRODUCTION

Androgen-suppression therapy (AST) is now widely used in combination with definitive radiotherapy for treatment of localized prostate adenocarcinoma (LPA). Randomized studies have demonstrated improved cure rates with the use of AST in combination with external-beam radiotherapy (EBRT) in patients with locally advanced or intermediate-risk to high-risk LPA (1, 2). AST can be given in a neoadjuvant fashion before EBRT, with the benefits of causing tumor and prostate gland shrinkage, inducing apoptosis, and enhancing tumor radiosensitivity (3).

Anemia is a well-recognized complication from AST, particularly with the use of leutenizing hormone–releasing hormone (LHRH) agonists (4, 5). AST produces castrate levels of circulating testosterone, and testosterone has a permissive effect on stimulating erythropoiesis through synergistic interactions with erythropoietin (6–8).

Malignant cells tend to be more hypoxic than their normal-cell counterparts, and hypoxic cells are more resistant

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Presented at the Multidisciplinary Prostate Cancer Symposium, Orlando, Florida, February 17, 2005.

Funded by Ortho Biotech Canada, (Toronto, Ontario, Canada), a division of Janssen-Ortho, Inc.

Received Oct 28, 2005, and in revised form Jan 17, 2006. Accepted for publication Feb 4, 2006.

to cell kill compared with well-oxygenated cells when exposed to therapeutic radiation. Recent studies that used microelectrode measurements of intraprostatic tissue-oxygen levels have shown that regions that bear prostate adenocarcinoma cells are hypoxic (9, 10). Anemia exacerbates tumor-cell hypoxia, and the presence of anemia during or before EBRT for other malignancies such as carcinoma of the cervix, head-and-neck, and lung has been shown to have a detrimental effect on tumor control and survival (11–14). Clinical data regarding the effects of tissue hypoxia and anemia on efficacy of EBRT for prostate adenocarcinoma are limited (15–17).

The purpose of this study is to determine the effect of hemoglobin (Hb) levels on treatment outcome in patients treated with neoadjuvant AST (NAST) and EBRT for LPA.

METHODS AND MATERIALS

Patient population

Between January 1976 and September 2000, 889 men with LPA were treated with EBRT and AST at the British Columbia Cancer Agency–Vancouver Island Centre. The cancer agency charts and electronic health records of these patients were reviewed. Five hundred sixty-three patients who received NAST + EBRT had Hb levels recorded before or during EBRT and are the subject of this retrospective analysis. Patients had 1997 American Joint Committee on Cancer clinical Stage T1 to T4, N0 to NX, and M0 to MX histologically confirmed adenocarcinoma of the prostate gland. All patients underwent history and physical examination, including digital rectal examination, pretreatment serum prostate-specific antigen (iPSA) testing, transrectal ultrasound–guided biopsies, or transurethral resection of prostate gland. Additional investigations including cystoscopy, CT scan, MRI scan, bone scan, and serum prostate-acid phosphatase were performed at the discretion of the oncologist and urologist, particularly for patients with intermediate-risk or high-risk features. For purposes of this study, patients were grouped into risk categories (e.g., low, intermediate, and high) on the basis of their iPSA, Gleason score, and clinical T stage according to the Canadian Genitourinary Radiation Oncology Group (CGRO) consensus on risk grouping for LPA. A minimum of 1 Hb measurement during NAST or EBRT was required for inclusion in this study. Patients were excluded from this study for the following reasons: previous radical prostatectomy, PSA follow-up after completion of EBRT less than 2 years, evidence of distant or nodal metastases at presentation, no Hb value during NAST or EBRT, no PSA before start of treatment, total duration of NAST less than 1 month.

Treatment

All patients received NAST for a minimum of 1 month before EBRT. Forty-six percent of men also received concurrent AST and 25% received further adjuvant AST after EBRT. A variety of hormone medications were used, including LHRH agonists (e.g., leuprolide, goserelin, and buserelin), nonsteroidal antiandrogens (flutamide, bicalutamide, and nilutamide), steroidal antiandrogens (cyproterone), diethylstilbestrol, and megestrol. The type of hormone agents used was at the discretion of the physician and generally depended on what was available on the cancer agency formulary. Some patients received various hormone combinations in a sequential fashion. In total, 44% received LHRH agonists, 59% received nonsteroidal antiandrogens, 49% received cyproterone, 32% received diethylstilbestrol, and 1% received megestrol. Twenty-eight percent had antiandrogen monotherapy as their AST. None of the patients received erythropoietin enhancers (e.g., epoetin alfa) or packed red blood cell transfusions during treatment.

EBRT consisted of multifield arrangement (e.g., 4-field 'box' technique) that used high-energy photons to encompass the prostate-gland region. The majority of men, particularly in later years, were planned by use of CT simulation and conformal-planning techniques. Four percent of men received pelvic-field irradiation with the intent of encompassing the pelvic lymph nodes at risk. The median cumulative dose was 66 Gray (Gy), with doses ranging between 48 Gy and 70 Gy in 2.75-Gy to 1.72-Gy fraction sizes. Patients who received pelvic-field treatment received a median dose of 46 Gy to the pelvis (range, 40–50 Gy). Cumulative EBRT doses were converted into biologic equivalent dose (BED) by use of the equation BED = total dose $\times$ [1 + (fraction size/ α/β ratio)] to allow comparisons between different doses and its impact on clinical outcomes. Alpha/beta ratio of 3 was selected, as literature suggests that this value is an appropriate ratio for prostate adenocarcinoma (18, 19).

Blood tests

Initial serum PSA (iPSA) levels were obtained on all patients before start of NAST and after EBRT and AST for a minimum of 2 years. Testosterone levels were inconsistently measured and are not reported in this analysis. Although testosterone levels were not consistently measured, most patients in this study would have achieved recovery or stabilization of their testosterone levels, as the median time to recovery after AST is approximately 10 months (20) and the minimum follow-up time required for this study was 2 years after EBRT.

Three hundred twenty-seven patients had Hb levels recorded before starting NAST (i.e., pre-NAST Hb). For patients who had multiple Hb measurements drawn before NAST, the most recent Hb before starting NAST was used to define the pre-NAST Hb. Five hundred twenty-four patients had Hb levels recorded before start of EBRT (i.e., pre-EBRT Hb). In patients who had multiple pre-EBRT Hb levels, the Hb that corresponded to the closest date of Hb drawn to the start of EBRT was used to define pre-EBRT Hb. Five hundred patients had Hb levels recorded during EBRT. In patients who had multiple Hb levels drawn during EBRT, the lowest Hb value during EBRT was used to define the Hb nadir during EBRT. The lower limit of normal range of Hb level was 13.5 g/dL and values below this limit were used to define anemia. The change in Hb was calculated as (pre-EBRT Hb)−(Hb nadir during EBRT) and as (pre-NAST Hb)−(Hb nadir during EBRT).

Follow-up

Follow-up time was calculated from the start of NAST. A minimum follow-up time of 2 years after completion of EBRT was required. Follow-up investigations included history and physical examination, including digital rectal examination and serum PSA measurement. Blood tests for testosterone and Hb were not routinely ordered after completion of EBRT. Interval between follow-up visits or blood tests was at the discretion of the physicians and was generally every 6 months or 1 year.

Statistical methods

The primary endpoint was time to PSA or biochemical failure (BF) from the start of NAST. A recent debate has arisen on the