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Intrarectal Amifostine During External Beam Radiation Therapy for Prostate Cancer Produces Significant Improvements in Quality of Life Measured by EPIC Score

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Abstract

Purpose—To test whether intrarectal Amifostine limits symptoms of radiation proctitis as measured by the RTOG GI toxicity score and the expanded prostate cancer index composite (EPIC) score.

Methods and Materials—Patients with localized prostate cancer recieved Amifostine as a rectal suspension 30–45 min before daily 3D-conformal radiation treatments (3D-CRT). The first 18 patients received 1gm of Amifostine and the next 12 patients received 2gm. Toxicity was assessed at baseline, during treatment, and at follow-up visits using RTOG grading and the EPIC Quality of Life (QoL) 50 item questionnaire. The “Bowel Function” subset of the bowel domain (EPIC-BF), which targets symptom severity, and “Bowel Bother” subset of the bowel domain (EPIC-BB), which assesses quality of life, were evaluated and compared to the RTOG GI toxicity score.

Results—Median follow-up was 30 months (range 18–36). Overall, the EPIC-BF and EPIC-BB scores both track closely with the RTOG GI toxicity score. Seven weeks after the start of radiation therapy, the incidence of RTOG Grade 2 toxicity was 33% in the 1gm group (6/18) compared with 0% (0/12) in the 2gm group and trended towards statistical significance (p=0.06). A significant difference between Amifostine groups was observed using the EPIC-BF score at 7 weeks (p=0.04). A difference in EPIC-BB score between dose groups was evident at 7 weeks (p=0.07) and was significant at 12 months (p=0.04).

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No authors had any conflict of interest to report.

Conclusions—Higher doses of Amifostine produce significant improvements in acute and late bowel QoL (up to one year following therapy) as measured by the EPIC score.

Keywords

Amifostine; Prostate; Radiation-induced Proctitis; EPIC; Quality of Life

Introduction

There are over 200,000 new cases and nearly 30,000 deaths each year from prostate cancer (1). Radiation therapy (RT) is a mainstay of local therapy, and it is known that biochemical disease free survival improves with dose escalation to the prostate (2,3).

Advances in methods of precise radiation dose delivery, such as 3D-Conformal Radiotherapy (3D-CRT) and Intensity Modulated Radiation Therapy (IMRT), have allowed higher radiation doses (dose escalation) to the prostate while minimizing toxicity by limiting the amount of normal tissue irradiated. Even with precise RT, however, the high dose radiation volume must include the anterior rectal wall to avoid under-dosing the periphery of the prostate. Consequently, if the radiation tolerance of the rectum can be improved, toxicity from therapy at current doses may be diminished and further dose escalation may be possible.

Amifostine is a radioprotector with the potential to improve radiation tolerance of the rectum. Amifostine has been tested in multiple solid tumor systems using several methods of delivery (4–9). Endorectal administration of Amifostine has been assessed in preclinical and pilot clinical trials (10–14).

There are several measures of radiation-induced toxicity. RTOG acute and late gastrointestinal (GI) toxicity is assessed in most current trials and comprises a grading system with scores ranging from 0–5 that are assigned by the physician based on the patient's symptoms and when the assessment is being made relative to the course of radiation. Newer tools for toxicity assessment have been developed that focus more on the patient's own assessment of their symptoms, and the change in their overall, and treatment-specific quality of life. We used one such measure, the Expanded Prostate Cancer Index Composite (EPIC) self-assessment questionnaire, in this trial. The EPIC score has been used to measure QoL in the acute and late setting (15–19).

This trial was undertaken to assess the effectiveness and dose-response of daily topical administration of Amifostine in reducing acute and late rectal toxicities in prostate cancer patients treated with 3D-CRT. In a previous publication, we reported acute toxicity profiles using the RTOG grade(20). We noted that use of instruments more sensitive than the RTOG grade may discriminate small but clinically important reductions in proctitis. This analysis was performed to report late toxicity outcomes in patients who received 1 or 2 gm daily endorectal Amifostine during treatment.

Methods

Eligibility and Accrual

All patients underwent history and physical examination as well as routine blood work including CBC, PSA, and alkaline phosphatase. Imaging studies such as bone scan were obtained as warranted. Eligible patients had localized adenocarcinoma of the prostate and were candidates for definitive or post-operative external beam radiotherapy. One patient in each group received post-operative radiation therapy. Use of adjuvant hormonal or experimental PSA vaccine therapy was permitted. All eligible prostate cancer patients evaluated for radiation

therapy at the National Cancer Institute were informed about this study. At the time of enrollment, all patients provided written, informed consent for participation in this IRB approved protocol.

Radiation Therapy

All patients underwent computed tomography simulation. Prior to simulation, liquid contrast, of equivalent volume to the amifostine suspension, was instilled endorectally. The prostate, rectum, and bladder were contoured using treatment planning software. The rectum was contoured from the anus (at the level of ischial tuberosities) to a length of 15 cm or until the rectosigmoid flexure could be identified. The clinical target volume (CTV) and the decision to treat the pelvic lymph nodes and seminal vesicles were based on clinical exam findings and whether the risk of involvement was greater than 15% as determined by the Roach equations using Gleason score and pretreatment PSA. 3D-CRT was delivered to all patients. The planning target volume (PTV) was defined as the CTV plus a margin ranging from 0.5 to 1.5 cm at the discretion of the treating physician. The plan was evaluated based on dose-volume-histogram analysis. No more than 25% of the rectal volume was allowed to receive 70 Gy. The prescription dose ranged from 72 to 76 Gy in 2 Gy fractions for most patients. The PTV was covered by at least 97% of the prescribed dose. The 2 post-operative patients received 66 Gy.

Amifostine Application

Amifostine (MedImmune, Inc., Gaithersburg, MD) was reconstituted in saline at a concentration of 50 mg/mL. The first 18 patients enrolled received a 1gm dose (20mL) of Amifostine, while the second cohort was given a 2 gm dose (40mL). Patients were aware of the dose of Amifostine they were receiving, but were not aware of the results of other patients enrolled in the study. Amifostine was administered endorectally at a low pressure using a 60cc syringe 30–45 minutes prior to each daily radiation treatment. The Amifostine preparation used was the same formulation used for intravenous administration and was not specifically formulated for this study. The first 15 patients were alternated between prone and lateral positions every 15 minutes after administration of Amifostine and the remaining 15 patients remained prone for 15 minutes after administration then were allowed to sit upright until radiation treatment. Intrarectal retention of less than 30 minutes was considered inadequate for dosing and documented as such, but this rarely occurred.

On Treatment and Follow-up Evaluations

Patients were evaluated by a physician weekly while on treatment. Upon completion of therapy, follow-up visits occurred at 6 weeks, 3 months, 6 months, then every 6 months until 3 years, and annually thereafter. Formal toxicity measures were assessed and recorded at baseline, at weeks 5 and 7 of therapy, and at each follow-up visit.

Measures of Radiation Related Rectal Injury

At each assessment, an RTOG toxicity score was assigned by the evaluating physician and the EPIC self-assessment questionnaire was completed by the patient. RTOG Acute Radiation Morbidity criteria were used for evaluations conducted during radiation treatment or within the first 90 days following treatment. RTOG Late Radiation Morbidity was used for assessments made greater than 90 days after completion of radiation treatment (See Table 1).

The EPIC questionnaire consists of 50 questions divided into four domains (Urinary, Bowel, Sexual, and Hormonal). Within the Bowel Domain, a subset of “Bowel Function” questions target symptom severity while “Bowel Bother” questions assess GI-related quality of life (See Table 2). The questionnaire is scored on a scale of 0–100 with higher scores correlated with higher function and quality of life. For this study, the Bowel Domain was analyzed alongside

the RTOG acute and late gastrointestinal morbidity scores. Questionnaires completed by the patients were scored using the SAS software and a scoring macro available from the University of Michigan (http://roadrunner.cancer.med.umich.edu/epic/epicmain.html).

Results of proctoscopic examinations with scoring of mucosal damage were reported using a descriptive scale, described by Wachter et al.(21) Proctoscopic exams were continued until an interim analysis revealed that, in this cohort, this instrument was not useful in the acute setting (15).

Statistical Analysis

Summary statistics, such as sample proportions, means, and median values were used to describe the patient characteristics. A two-sided Fisher's exact test was used for comparing proportions across groups. A Wilcoxon rank sum test was used to compare medians across groups for continuous variables. All analyses were performed with MATLAB software (The Mathworks, Inc, Natick, MA, USA).

Results

Thirty consecutive patients with localized prostate adenocarcinoma were enrolled on this trial. Median follow-up was 30 months (range 18–36). As shown in Table 1, the 1gm and 2gm groups were similar for most patient, tumor, and treatment characteristics. Median age, however, was 69 and 62 respectively (p=0.01) (Table 3). Amifostine treatment was generally well tolerated. No patient reported any local or systemic toxicity, other than one patient who reported "a metallic taste" following administration of the drug.

For this analysis, the EPIC Bowel Function (EPIC-BF) composite score, EPIC Bowel Bother (EPIC-BB) composite score, and the acute and late RTOG GI toxicity scores were compared for all enrolled patients. Using both RTOG and EPIC scores, at all assessment points there is a clear trend towards increased rectal protection with the 2 versus 1gm Amifostine. As has been previously reported, 7 weeks after the start of radiation therapy, the incidence of RTOG Grade 2 toxicity was 33% in the 1gm group (6/18) compared with 0% (0/12) in the 2gm group revealing a trend towards increased protection with the 2gm dose (Figure 1) which does not achieve statistical significance (p=0.06).(20) As shown in Figure 2, a significant difference between Amifostine dose groups was observed using the EPIC-BF score at 7 weeks (p=0.04). A difference in EPIC-BB score between dose groups (Figure 3) was also evident at 7 weeks (p=0.07) and was significant at 12 months (p=0.04).

For each dose group, the mean EPIC scores tend to track each other across time. Further, changes in mean EPIC scores tend to track changes in mean RTOG scores (in a reverse fashion) over time. Further, although a true correlation cannot be calculated since RTOG scores range from 0–4 and EPIC scores range from 1–100, the changes in mean EPIC scores tend to track changes in mean RTOG scores (in a reverse fashion) over time.

Discussion

Our results provide evidence of diminished rectal toxicity with 2 versus 1 gm intrarectal Amifostine. This trend nears significance at the end of therapy (7 weeks) using the RTOG grading system. However, using the EPIC-BF and EPIC-BB scores, at all assessment points there is a clear trend towards improved bowel-related QoL with 2 versus 1 gm intrarectal Amifostine. This trend reached significance (p=0.04) at seven weeks of treatment with the EPIC-BF and at 12 months of follow-up with the EPIC-BB (p=0.04). The improvement in bowel-related QoL with 2 versus 1 gm intrarectal Amifostine appears to be durable at least one year following treatment.

The EPIC score was developed at the University of Michigan as an expansion of the UCLA Prostate Cancer Index and has been validated as a robust instrument that offers a comprehensive assessment of health-related quality of life.(16) EPIC has now been used in several studies to evaluate patient reported health-related QoL outcomes in the management of prostate cancer (17–19).

The findings of this study also suggest that the EPIC score is a sensitive measure to detect changes in both acute and late bowel-related QoL associated with radiation treatment for prostate cancer. The ability to detect even small improvements in radiation-induced side effects is important since it is now clear that treatment of prostate cancer with conventional radiation therapy results in biochemical disease free survival that corresponds predictably to the dose of radiation administered (2,3). However, increasing radiation dose can produce increased rectal toxicity as well. Acute radiation-induced proctitis can manifest during or after a course of radiation treatment and can include bleeding, rectal pain, mucoid discharge, and fecal urgency. While acute side effects occur within 120 days after completion of treatment, the patient may also experience late radiation-induced proctitis which can be permanent and may include tenesmus, persistent diarrhea, hematochezia, and rectal or anal strictures.

As described more fully in our previous publication (20), several studies have assessed whether the administration of Amifostine prior to radiation therapy confers normal tissue protection. Intravenous Amifostine was shown to decrease the number of patients with RTOG Grade 2 or greater toxicity by approximately 15%, however it is not well tolerated due to hypotension, nausea and rashes (22–25). Subcutaneous administration of Amifostine is better tolerated, but still causes nausea and a fever/rash (7,23,26). With regard to rectal mucosal protection, however, subcutaneous administration is inferior to daily topical administration of Amifostine (23).

In a rat model, Ben-Josef et al described preferential accumulation of Amifostine and the active dephosphorylated metabolite in the rectum and not the prostate after intrarectal administration of Amifostine (11). Ben-Josef et al later studied 29 prostate cancer patients treated with Amifostine dose levels ranging from 0.5 to 2.5gm in 40 to 50mL solution, applied before the first 15 radiation treatments. Pharmacokinetic studies were performed on days 1 and 10 of treatment. Neither free parent compound nor free active metabolite was detected in the systemic circulation and, consistent with our findings, there was no systemic toxicity. The authors found that late rectal bleeding developed significantly more often in patients receiving 0.5 to 1gm than in patients receiving 1.5 to 2.5gm Amifostine (50% *v* 15%; $p = 0.0325$) (12). These results support our finding that 2 versus 1gm of Amifostine has greater efficacy in reducing late radiation proctitis.

Although very few patients experience RTOG Grade 3 or higher toxicity following external beam radiation therapy (27), even mild rectal toxicity can be detrimental to quality of life. Therefore, the efficacy interventions to reduce rectal toxicity must be measured by sensitive quality of life instruments. Traditionally, the RTOG acute and late GI toxicity scores have been assigned by the examining physician. More recently, the EPIC survey has been employed which utilizes a questionnaire completed by the patient allowing for a more comprehensive assessment of the patient's symptoms and eliminates physician bias. This includes small but important changes in QoL that might not be apparent during brief questioning by a physician or represented by scoring on the broad 0 to 5 RTOG scale.

Perhaps as a result of this ability to discriminate smaller changes, the EPIC-BF and EPIC-BB scores demonstrated significant differences in acute and late GI toxicity in patients treated with 1gm compared to 2gm of Amifostine. Nonetheless, as both the RTOG and EPIC scores are

dependent on patient reporting, a high correlation between these measures should be expected and, indeed, was observed in this study.

Conclusion

A higher dose of intrarectal Amifostine, 2gm versus 1gm, produces significant improvements in acute and late bowel QoL as measured by the EPIC score and a trend towards significant improvement in RTOG GI toxicity score. Improvements in QoL persist up to one year following therapy.

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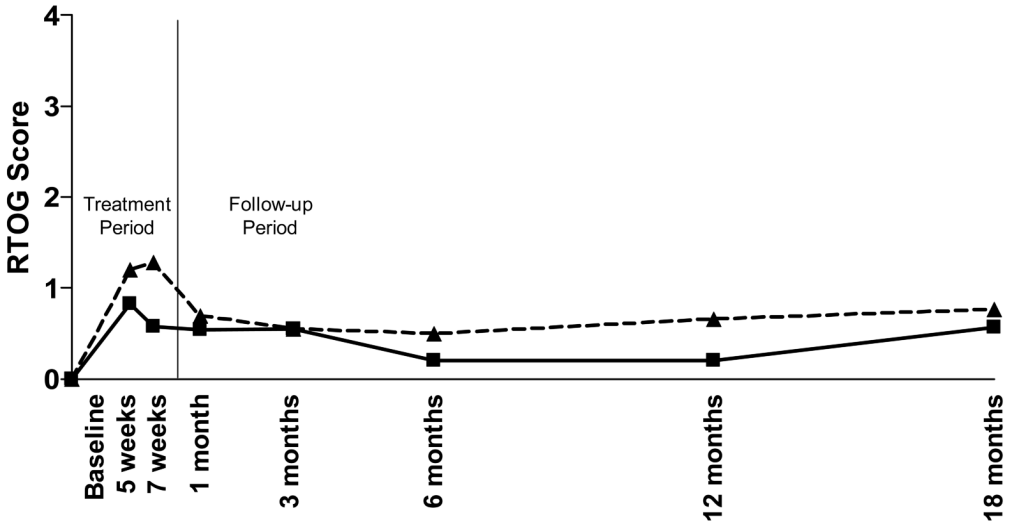

Figure 1. RTOG GI Toxicity Score

RTOG toxicity was determined at each pre-determined time point for the patients in each group. Mean RTOG scores are presented by dose. Patients who received 1gm Amifostine (---△---) had slightly higher, but not significantly different RTOG scores than the patients who received a 2gm dose (—□—).

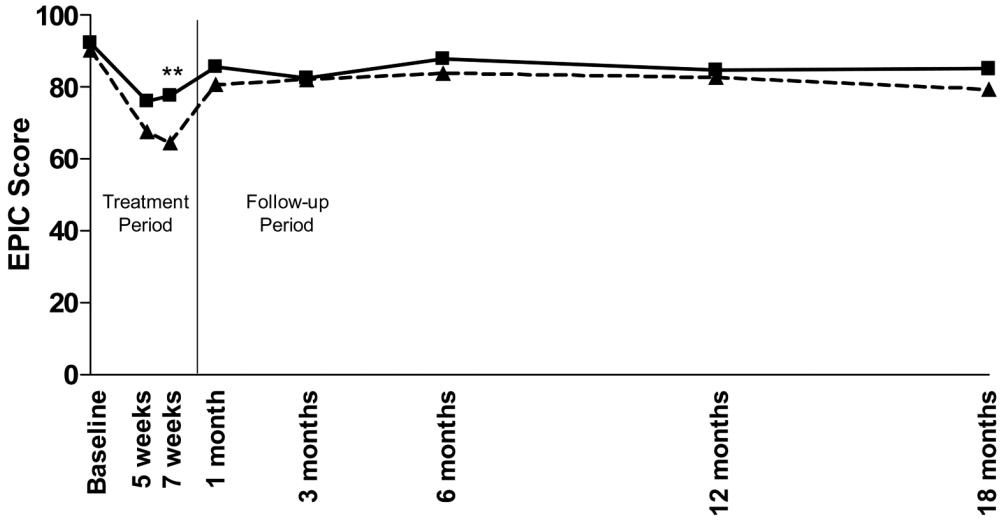

Figure 2. EPIC-Bowel Function Composite Score

EPIC-BF toxicity was determined at each pre-determined time point for the patients in each group. Mean RTOG scores are presented by dose. Patients who received 1gm Amifostine (---△---) had slightly higher, EPIC scores than the patients who received a 2gm dose (—□—). This difference was significant (p=0.04) at the 7-week time point (denoted by **).

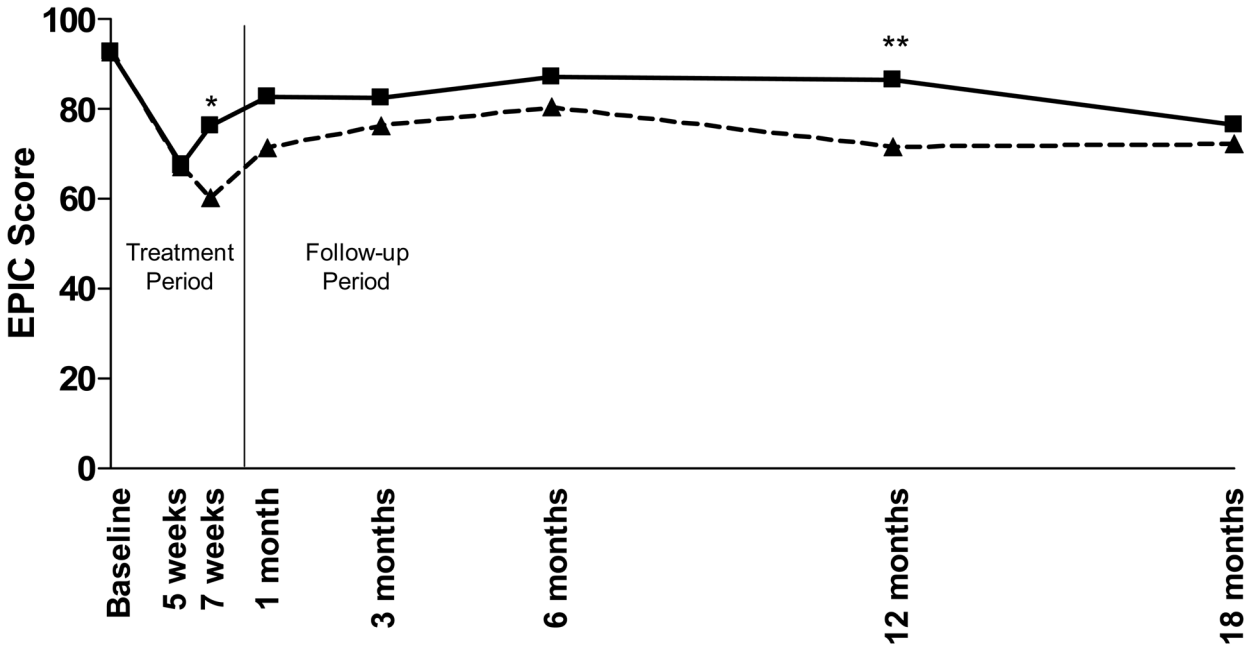

Figure 3. EPIC-Bowel Bother Composite Score

EPIC-BB toxicity was determined at each pre-determined time point for the patients in each group. Mean RTOG scores are presented by dose. Patients who received 1gm Amifostine (---△---) had slightly higher, EPIC scores than the patients who received a 2gm dose (—□—). This difference was nearly significant (p=0.07) at the 7-week time point (denoted by *) and achieved statistical significance (p=0.04) at 12 months (denoted by **).

Table 1

RTOG Toxicity Scoring Criteria

	Acute Toxicity (<120 days)	Late Toxicity (>120 days)
Grade 1	Increased frequency or change in quality of bowel habits not requiring medication Rectal discomfort not requiring analgesics	Mild diarrhea or cramping Bowel movement up to 5 times daily Slight rectal discharge or bleeding
Grade 2	Diarrhea requiring a parasympatholytic drug Mucous discharge not necessitating sanitary pads Rectal or abdominal pain requiring analgesics	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding
Grade 3	Diarrhea requiring parenteral support Severe mucous or blood discharge needing sanitary pads Abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Obstruction or bleeding requiring surgery
Grade 4	Acute or subacute obstruction, fistula, or perforation GI bleeding requiring transfusion Abdominal pain or tenesmus requiring tube decompression or bowel diversion	Necrosis Perforation Fistula

Table 2

EPIC Bowel Domain Questions

How often have you had rectal urgency (felt like you had to pass stool, but did nothing) during the past 4 weeks?
How often have you had uncontrolled leakage of stool or feces during the past 4 weeks?
How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) during the past 4 weeks?
How often have you had bloody stools during the past 4 weeks?
How often have your bowel movements been painful during the past 4 weeks?
How many bowel movements have you had on a typical day during the past 4 weeks?
How often have you had cramping pain in your abdomen, pelvis or rectum during the past 4 weeks?
How big a problem, if any, has each of the following been for you? **a.** Urgency to have a bowel movement **b.** Increased frequency of bowel movements **c.** Watery bowel movement **d.** Losing control of your stools **e.** Bloody stools **f.** Abdominal/ pelvic/ rectal pain
Overall, how big a problem have your bowel habits been for you during the past 4 weeks?

Table 3

Patient Demographics

	1 gm Group	2 gm Group	*p*-value
Median Age	69	62	0.01
Median Follow-up	19 months	17 months	NS
Clinical Stage T2a or less	89% (16 of 18)	83% (10 of 12)	NS
Median Gleason Score 6 or less	22% (4 of 18)	33% (4 of 12)	NS
PSA Less than 10	89% (16 of 18)	83% (10 of 12)	NS
Median Radiation Dose (Gy)	74	74	NS
Largest Field Treated			
Prostate + Pelvis	44% (8 of 18)	42% (5 of 12)	NS
Prostate + Seminal Vesicles	28% (5 of 18)	25% (3 of 12)	NS
Prostate only	28% (5 of 18)	33% (4 of 12)	NS
Mean % volume of rectum at 50 Gy	50	45	NS
Mean % volume of rectum at 70 Gy	17	16	NS
Concurrent Hormone Therapy	56% (10 of 18)	66% (8 of 12)	NS