Brachytherapy and Continuous Infusion 5-Fluorouracil for the Treatment of Locally Advanced, Lymph Node Negative, Prostate Cancer

A Phase I Trial

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BACKGROUND. 5-fluorouracil (5-FU) is a known radiosensitizer that enhances efficacy, in vivo and in vitro, when administered during radiotherapy. The following study was performed to evaluate the toxicity of continuous infusion 5-FU administered concomitant with brachytherapy in patients with locally advanced prostate cancer.

METHODS. Over a 26-month period, a total of 25 patients with newly diagnosed, locally advanced prostate cancer underwent radioactive gold (Au^{198}) brachytherapy. Twenty-four of 25 patients were surgically staged and confirmed node negative. Au^{198} seed placement was performed transperineally under fluoroscopic and ultrasonographic guidance using an average of 195 mCi of Au^{198}. Within 4 hours after seed placement, 25 patients received 5-FU administered as a continuous infusion over 4 days, at 1 of 8 dose levels ranging from 200–1100 mg/m^2/day. Patients had clinical follow-up for a minimum of 1 year. Decreases in serum prostate specific antigen (PSA) and prostate volume (normalized to pretreatment values) were determined at 12 months.

RESULTS. 5-FU associated toxicity was negligible, with Grade 1 nausea in four patients and no Grade 2 or higher toxicity. No unique locoregional toxicity was noted. At 12 months after treatment, PSA values decreased on average to 16.4% of pretreatment values. Twelve-month prostate volumes decreased to 55% of the pretreatment values.

CONCLUSIONS. These findings suggest that continuous infusion 5-FU can be administered safely concomitant with brachytherapy at doses up to 1100 mg/m^2 per day for 4 days. ***Cancer* 1996; 77:924–7.** © *1996 American Cancer Society.*

KEYWORDS: brachytherapy, prostatic neoplasms, 5-fluorouracil, radiosensitizer, infusion.

The optimal therapy for organ-confined prostate cancer remains controversial. In patients with clinically organ-confined disease undergoing radical prostatectomy, 5- and 10-year prostate specific antigen (PSA) recurrence free survival has been reported to range from 69–88% and 47–70%, respectively. Patients with established capsular penetration have significantly higher rates of PSA and clinical recurrence.[1,2] Patients undergoing external beam radiotherapy for clinically organ-confined disease have PSA relapse free survival rates reported from 41–92% with 3–5 years of follow-up.[3] These figures underscore the need for more effective treatment strategies for carcinoma of the prostate.

Recent developments in brachytherapy have led to a renewed interest in this technique as a treatment modality for localized prostate cancer. Historically, brachytherapy as an alternative means of delivering

radiotherapy has been utilized since the early 1900s, using either iodine, gold, iridium and, more recently, palladium as the source. Advances in imaging technology and source placement have overcome the inhomogeneous dosimetry that plagued early trials. By eliminating "cold" spots and decreasing the radiation dose to adjacent normal tissue, brachytherapy as currently practiced promises better local control with fewer side effects.[4,5]

Although brachytherapy may allow higher radiation doses to be delivered to the tumor, it is unlikely that this approach alone will prove to be a panacea for localized prostate cancer. One strategy to improve the therapeutic outcome of radiotherapy is the concomitant administration of chemotherapy agents utilized as radiation potentiators. 5-fluorouracil (5-FU) is a well recognized radiosensitizer,[6] but it has limited single agent activity in metastatic prostate cancer.[7,8] The goal of the present study was to determine if 5-FU can be safely administered as a continuous infusion concomitant with brachytherapy.

MATERIALS AND METHODS

Study Group

Between July 1991 and September 1993, a total of 25 patients with newly diagnosed, locally advanced prostate cancer were enrolled in a Phase 1 trial of brachytherapy employing radioactive gold (Au^{198}) and continuous infusion 5-FU. A Phase I design was chosen due to the potential for radiation sensitizers to increase not only tumoricidal activity but also local toxicity (radiation proctitis and fistulas), and the lack of previously reported experiences combining these modalities for the treatment of prostate cancer. All patients were assessed initially by physical examination, laboratory studies, PSA (Tandem-R, Hybritech, San Diego, CA), prostatic acid phosphatase (enzymatic assay), bone scan, and transrectal ultrasound. Twenty-four of the 25 patients were surgically staged and confirmed lymph node negative. Eligibility criteria for participation in the 5-FU trial included histologic confirmation of adenocarcinoma of the prostate; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; clinical stage Tx,N0,M0;[9] no prior pelvic radiotherapy; adequate hematologic, renal, and hepatic function; and written informed consent.

Radioactive Seed Placement

Radioactive gold seeds were implanted via a transcutaneous, transperineal approach with the patient in the lithotomy position and anesthetized with either general endotracheal or spinal anesthesia. Mick applicator guns (Mick Radio Nuclear Instruments, Inc., Bronx, NY) were used to deliver the seeds into the prostate, using simultaneous high resolution fluoroscopy and transrectal ultrasonography. This technique has been described previously.[10] Postoperatively, the distribution of the radioactivity within the pelvis was assessed by our radiotherapy department by means of a three-dimensional dosimetric analysis using a method previously described to ascertain the cumulative amount of radiation delivered to the prostate.[11] This technique is advantageous in that it provides a view of the entire dose distribution at once in relation to anatomic structures, from any perspective, and allows structures that impede visualization of the target organ to be removed or made transparent. Isodose curves ranging from 0–20,000 cGy can be viewed from within the organ of interest.

Patients remained in radiation isolation until the level of radioactivity was less than 5 millirems (mrem) per hour measured at 1 meter from the patient. If the implant did not deliver 100 cGy matched peripheral dose (MPD), supplemental external beam radiation was given to the extent deemed safe, respecting the tolerance dose of the rectum, up to 5 weeks following completion of brachytherapy.

Chemotherapy

5-fluorouracil was administered as a continuous infusion starting within 4 hours of Au^{198} seed placement and was continued for 96 hours. Because the implant delivers doses exceeding 70 cGy to portions of the rectum, a very conservative 5-FU dose escalation schema was utilized, starting at 200 mg/m^2 and escalating by 100 mg/m^2 to 700 mg/m^2, then 900 and 1100 mg/m^2. A minimum of three patients were treated at each dose level. A minimum of 4 weeks were required to elapse from the time the last patient entered at each dose level to determine the degree of toxicity prior to dose escalation. The maximally tolerated dose was defined as the dose causing Grade 3 nonhematologic toxicity in more than one-third of patients. Toxicity was assessed by common toxicity criteria.

RESULTS

The characteristics of patients in the study group are shown in Table 1. The median patient age (67.9 years) of this group is typical of prostate cancer. Nine patients had clinical Stage T2, six Stage T2–3, and 10 Stage T3 disease. The mean Gleason score was 6.2 and mean PSA was 16.7. Twenty-three patients (92%) underwent either open or laparoscopic pelvic lymph node staging. Two patients had received a brief course of a luteinizing hormone-releasing hormone antagonist and flutamide in an effort to downstage their disease.

The mean amount of radioactivity administered per patient was 195.5 mCi with a range from 168.7 to 211.6 mCi. The mean number of Au^{198} seeds implanted per patient was 49.7 (range, 38–64 seeds) and the mean radioactivity per seed was 4.07 mCi (range, 2.95–5.29 mCi). Three-dimensional dosimetry demonstrated that the MPD was 100 Gy in 10 patients, 70 Gy in 12 patients, and 50 Gy in 3 patients. All 3 patients with 50 Gy MPD and the 4 patients with 70 Gy MPD had supplemental external

TABLE 1
Patient Characteristics

Age	67.9 ± 6.5*
Gleason score	6.2 ± 1.3
4	2 (8%)
5	5 (20%)
6	9 (36%)
7	5 (20%)
8	3 (12%)
9	1 (4%)
PSA	16.7 ± 23.3
≤ 4	5 (20%)
> 4, ≤ 10	9 (36%)
>10	11 (44%)
Prostate volume (cc)	36.3 ± 14.3
Clinical Stage	
T2	9 (36%)
T3	16 (64%)
mCi Au^{198}	198 ± 8

PSA: prostate specific antigen.
Values are reported as the mean ± one standard deviation or the number of patients in a given category (percentage of total group).

beam radiation. The total dose to the periphery of the prostate ranged from 70–100 Gy, with a mean of 85.9 Gy and a median of 90 Gy. The initial dose rate varied from 53.6–107 cGy per hour, with a mean of 85.3 cGy per hour.

The study was halted at the 1100 mg/m^2 5-FU level prior to achieving dose-limiting toxicity. Overall toxicity was negligible with no Grade 2 or higher event. Two patients developed Grade 1 leukopenia at the 500 and 700 mg/m^2/day levels, respectively. There was no Grade 1 thrombocytopenia. All patients experienced Grade 1 self-limited radiation cystitis. Four patients had Grade 1 nausea.

Twelve months after seed implantation, patients who received concomitant 5-FU had an average decrease in their serum PSA to 16.4% ± 11.2% (± one standard deviation) of their pretreatment value. Prostatic volumes 12 months after treatment decreased to 55.4% ± 29.5% of pretreatment values in the study group. No additional, unique, locoregional toxicity was noted during the 12-month follow-up interval.

DISCUSSION

Fluorouracil is a uracil analog that can bind to thymidylate synthase as 5-fluorodeoxyuridine monophosphate or undergo sequential phosphorylation and integration into RNA. After bolus administration, it has a short plasma half-life of 8–15 minutes. Clinical data would suggest that the pharmacokinetics and antitumor efficacy of 5-FU is improved by continuous infusion as compared with bolus delivery.[12] Patients with colon cancer reportedly have an increased response rate if treated with infusional versus bolus fluorouracil.[13] A recent multicenter trial demonstrated a significant improvement in survival of patients with rectal cancer treated with an infusional versus bolus schedule.[14] Continuous infusion 5-FU has shown mixed results in the treatment of metastatic hormone refractory prostate cancer.[7,8,15]

There is significant in vitro and in vivo data demonstrating increased cytotoxicity of radiation in the presence of 5-FU.[16,17] The cellular mechanism of 5-FU interaction with radiation has not been clearly identified. However, there is increasing evidence that 5-FU interferes with rejoining of radiation-induced DNA double strand breaks, or with recovery from potentially lethal damage.[18] By maintaining therapeutic serum concentrations during an ongoing period of radiation-induced DNA damage, continuous infusion 5-FU has significant theoretical advantages relative to bolus administration when used in combination with radiotherapy.

Continuous intravenous infusion of 5-FU with concurrent radiation had been tested in a variety of clinical settings, including gastric, pancreatic, biliary, esophageal, and anal cancer.[19–23] However, the use of this approach for prostate cancer, in combination with brachytherapy, has not been previously reported. Based upon a long-standing institutional interest and experience with Au^{198} prostate brachytherapy, and theoretical advantages of this isotope in combination with 5FU, we opted to perform a study of 5-FU in combination with Au^{198} brachytherapy.

The physical properties of various radioisotopes used in prostate brachytherapy has been the subject of a recent review.[4] Au^{198} has a photon energy of 412 kiloelectron volt (KeV), which is much greater than that of either palladium (Pd^{103}) at 21 KeV or iodine (I^{125}) at 28 KeV.[24] The higher photon energy of Au^{198} may make the precise placement of the seeds less critical than for the lower energy isotopes, but at the price of delivering a high dose to a larger portion of the rectum. In addition to the concerns about the physics of the radiation dose delivery based on deviations from the treatment preplan,[25] the relative biologic effectiveness of the various isotopes also warrants consideration.[26,27] For typical dose prescriptions of MPDs of 100 Gy for Au^{198}, 115 Gy for Pd^{103} and 160 Gy for I^{125}, the initial dose rates are 107 cGy per hour for Au^{198}, 19.6 cGy per hour for Pd^{103}, and 7.69 cGy per hour for I^{125}. There is good clinical evidence that the use of I^{125} is associated with inferior local control rates in patients with rapidly growing (high Gleason grade) prostate cancers, probably owing to the low dose rate.[28,29]

The combination of higher photon energy and dose rate of Au^{198} make it an attractive candidate for use in combination with continuous infusion 5-FU. However, given the dearth of data on this approach in prostate cancer, limited experience in other disease sites, and the potential of Au^{198} to deliver higher doses of radiation to the anterior rectal wall, we opted to perform a dose esca-

lation study of 5-FU in combination with Au^{198} brachytherapy. The dose range of 5-FU evaluated was based upon doses used in the majority of trials involving concomitant chemoradiotherapy with 5-FU as a radiosensitizer (500–1000 mg/m^2).[30,31]

A total of 25 patients were treated with escalating doses of 5-FU. The trial was stopped at a dose of 1100 mg/m^2 with essentially no hematologic or gastrointestinal toxicity. This data suggests that conventional doses of continuous infusion 5-FU can be safely administered concomitant with Au^{198} prostate brachytherapy.

CONCLUSIONS

Conventional doses of 5-FU can be administered safely as a continuous infusion concomitant with brachytherapy for prostate cancer.

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