Establishing Schedules for Repeated Doses of Strontium and for Concurrent Chemotherapy in Hormone-Resistant Patients With Prostate Cancer

Measurement of Blood and Urine Strontium Levels

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Abstract: Strontium-89 (Sr-89) alone or with concurrent chemotherapy has a role in the treatment of patients with prostate cancer (PCP). The schedules for repeated doses of Sr-89 or for concurrent chemotherapy is undetermined. The objective of this study was to measure the effective half-life (Te) of Sr-89 using a detector available in a nuclear research facility. Blood and urine samples obtained from PCP treated with Sr-89 (Metastron, Amersham, U.K.) were measured for radioactivity with a High Pure Germanium (HPGe) detector in a gamma spectrometry system (Eurisys, France). Twenty-five urine and 22 blood samples were obtained from 8 patients during a period of 160 days after Metastron injection. Sr-89 radioactivity levels in blood and urine were quite low ($<8.2 \times 10^{-3}$ μCi/mL) in all patients after 21 days, whereas Sr-85 (available in 0.5% of Metastron) urine and, to a lesser extent, blood radioactivity levels were moderately high and could be detected up to 160 days. Based on Sr-85 urine levels, the calculated Sr-89 Te ranged from 9.6 to 20.7 days. Sr-89 Te can be routinely calculated in PCP based on HPGe detection of Sr-85 radioactivity levels in urine. This measurement can establish schedules for either repeated doses of Sr-89 or concurrent chemotherapy.

Key Words: strontium 89, chemotherapy, blood levels, urine levels, prostate cancer

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Sr-89 has a palliative effect in the treatment of hormone-resistant patients with prostate cancer (PCP) with bony metastases.[1] Several phase II studies reported on its having a therapeutic advantage when it was given with concurrent chemotherapy.[2,3] Moreover, in a randomized study, Tue et al.[4] reported a longer overall survival over PCP treated with chemotherapy alone. The time during which the chemotherapy was delivered ranged from 6 weeks to 3 months,[4,5] and repeated doses of Sr-89 were administered over 3 to 6 months.[6,7] This timeframe depends on the biologic half-life (Tb) of Sr-89. In normal bone, the half-life is approximately 14 days, whereas it measures >50 days in reactive bone around metastasis.[8] At 90 days, the retention of Sr-89 ranged from a high of 88% (with significant metastatic involvement) to a low of 11% (with minimal involvement).[8] The currently available methods for measuring Sr-89 retention are based on bremsstrahlung imaging[9,10] and on the detection of Sr-85.[11–13] The bremsstrahlung scan has a good correlation with ordinary bone scan and does confirm Sr-89 deposition in the metastatic bones. It cannot, however, be used repeatedly to measure the time scale of Sr-89 clearance. A whole-body Sr-85 scan requires higher doses of Sr-85, which, in turn, has a detrimental effect on bone marrow as a result of Sr-85's pure gamma emission. Nevertheless, Giammarile et al.[14] used this Sr-85 isotope to treat PCP, although this approach did not gain wide clinical use. Bone-marrow suppression may occur 4 to 6 weeks after Sr-89 treatment,[15] after which repeated doses of Sr-89 might be considered. When Sr-89 is given concurrently with chemotherapy, however, it should be repeated with caution because the chemotherapy itself induces bone marrow suppression.

The wide range of Sr-89 retention (11–90% at 90 days)[8] in the body, the available but not generally used methods for Sr-89 detection, and the combination of this material with chemotherapy preclude the establishment of

accurate scheduling of repeated doses of Sr-89 or for the duration of chemotherapy.

One of the currently available Sr-89 products for medical use is Metastron (Amersham, U.K.). Based on the manufacturer's specifications, Metastron has <0.5% impurity of Sr-85. Sr-89, which is mainly a beta emitter, produces 909 KeV gamma rays at a very low yield, whereas Sr-85 produces gamma rays at an energy level of 514 KeV. Detection of such low doses of both Sr-89 and Sr-85 gamma emission is usually restricted to a well-equipped nuclear research facility.

The objective of this study is to measure the blood and urine levels of both Sr-89 and Sr-85 that are available in Metastron using a rather inexpensive device available in a nuclear research facility. We assume that by detecting Sr-89 and Sr-85 either in blood or urine, we will be able to accurately calculate the effective half-life (Te) of Sr-89 and, therefore, establish time schedules by which concurrent chemotherapy or repeated doses of Sr-89 can be given to responding patients.

MATERIALS AND METHODS

Patients who had hormone-resistant prostate cancer were enrolled in this study. They all had symptomatic bony metastases in at least 3 anatomic sites (including the head, rib cage, spine, pelvis, and others, based on bone scan uptake ± computed axial tomography scan findings ± plain bone films) requiring narcotics, as well as rising levels of prostate-specific antigen (PSA). The expected survival of all patients was at least 3 months. Blood and urine samples were obtained during a regular follow up after Sr-89 injection. The urine samples were obtained through a 24-hour urine collection.

Informed consent to participate was obtained from all patients, and this study was approved by the local ethics committee.

The injectable Sr-89 was supplied by Amersham Company (U.K.). We confirmed the manufacturer's specifications that Metastron has an impurity of <0.5% Sr-85 by measuring the radioactivity of a few drops in empty bottles. The Sr-89 was supplied in a small bottle containing 4 mL of the radioactive material. The injected Metastron dose in all patients was 4 mCi.

Blood and urine samples were measured for radioactivity using an HPGe detector in a gamma spectrometry system (Eurisys, France). This device has a minimal detectable activity (MDA) of 3.35×10^{-4} μCi/mL (12 Bq/mL) for Sr-89 and 3.23×10^{-8} μCi/mL (1.2 Bq/mL) for Sr-85 (with a counting time of 50,000 seconds). The appropriate MDA had been determined according to the actual time counting.

The patients' blood and urine levels of both Sr-85 and Sr-89 were measured at different time points. These levels were used to determine the Te (taking into account the known physical half-life [Tp] of both Sr-89 and Sr-85). The Tb could be calculated once the Te was known. Sr-85 and Sr-89 share the same Tb. The correlation among Te, Tb, and Tp is presented in the following equation:

$$Te = (Tp \times Tb)/(Tp+Tb)$$

RESULTS

Eight patients were enrolled to this study and their characteristics are presented in Table 1. A total of 25 urine and 22 blood samples were obtained from 8 and 7 patients, respectively, during a period of 160 days after Metastron injection. Four out of 8 patients were treated with concurrent gemcitabine in an ongoing phase I–II study.

Blood Studies

Sr-89 levels were less than 8.2×10^{-3} μCi/mL in all patients after day 21 (Table 2). Sr-85 levels above 1.2×10^{-6}

TABLE 1. Patients' Characteristics

Patient	Age (years)	Weight (kg)	No. of Tumor Sites	Chemo	WBC at Treatment (K/uL)	WBC at 6 wk (K/uL)	PLT at Treatment (K/uL)	PLT at 6 wk (K/uL)	Creatinine Level at Treatment (mg/dL)
1 (KB)	69	62	4	No	6.3	4.2	232	279	1.31
2 (HM)	81	76	4	No	5.5	3.8	181	131	1.27
3 (PG)	59	73	4	Yes	5.2	3.0	195	70	1.06
4 (LG)	57	85	5	No	5.6	4.1	242	236	0.7
5 (STD)	59	85	5	Yes	8.4	5.4	299	270	0.89
6 (KR)	70	91	4	Yes	8.9	3.3	210	73	1.21
7 (HJ)	77	69	7	Yes	4.7	2.5	201	60	1.47
8 (AD)	78	76	5	No	5.3	3.7	283	224	1.07

Chemo, chemotherapy; WBC, white blood count; PLT, platelets.

TABLE 2. Sr-85 and Sr-89 Blood Levels in Patients With Prostate Cancer Treated With Metastron

Patient	Time Postinjection (days)	Sr-85 Activity (μCi/mL)	Sr-89 Activity (μCi/mL)
1 (KB)	21	3.12×10^{-7}	$<(\text{MDA} = 8.2 \times 10^{-3})$
	73	$<(\text{MDA} = 1.4 \times 10^{-7})$	$<(\text{MDA} = 2.10 \times 10^{-3})$
2 (AH)	24	$<(\text{MDA} = 5.3 \times 10^{-7})$	$<(\text{MDA} = 1.6 \times 10^{-3})$
	80	1.04×10^{-7}	$<(\text{MDA} = 1.5 \times 10^{-3})$
3 (PG)	49	$<(\text{MDA} = 2.3 \times 10^{-7})$	$<(\text{MDA} = 3.7 \times 10^{-3})$
	77	$<(\text{MDA} = 2.3 \times 10^{-7})$	$<(\text{MDA} = 3.7 \times 10^{-3})$
4 (LG)	21	1.20×10^{-6}	$<(\text{MDA} = 3.7 \times 10^{-3})$
	49	7.61×10^{-7}	$<(\text{MDA} = 3.7 \times 10^{-3})$
	77	$<(\text{MDA} = 7.6 \times 10^{-7})$	$<(\text{MDA} = 3.7 \times 10^{-3})$
5 (STD)	35	8.10×10^{-7}	$<(\text{MDA} = 7.6 \times 10^{-3})$
	49	$<(\text{MDA} = 3.53 \times 10^{-7})$	$<(\text{MDA} = 8.2 \times 10^{-3})$
	84	2.66×10^{-7}	$<(\text{MDA} = 3.7 \times 10^{-3})$
	98	$<(\text{MDA} = 2.66 \times 10^{-7})$	$<(\text{MDA} = 1.6 \times 10^{-3})$
6 (KR)	21	1.46×10^{-6}	$<(\text{MDA} = 8.2 \times 10^{-3})$
	49	$<(\text{MDA} = 3.19 \times 10^{-7})$	$<(\text{MDA} = 1.6 \times 10^{-3})$
	78	$<(\text{MDA} = 2.81 \times 10^{-7})$	$<(\text{MDA} = 1.6 \times 10^{-3})$
7 (HJ)	20	1.78×10^{-6}	$<(\text{MDA} = 8.2 \times 10^{-3})$
	49	7.61×10^{-7}	$<(\text{MDA} = 1.6 \times 10^{-3})$

μCi/mL were detected in 3 patients after 21 days and above 1×10^{-7} in 2 patients after 70 days (Table 2).

Urine Studies

Sr-89 level less than 8.2×10^{-3} μCi/mL were detected in all patients after 21 days (Table 3). Sr-85 levels above 1×10^{-6} μCi/mL were detected in all patients after 21 days and in 2 patients after 70 days (Table 3). A level above 1×10^{-7} μCi/mL was detected in 1 patient after 148 days (Table 3).

Because the detection of urine Sr-85 level was possible over a prolonged period of time, we used this isotope to calculate the Tb (Table 4). The Sr-89 Te could be calculated based on the Tb value (Table 4). The Sr-89 Te ranged from 9.6 to 20.7 days.

Three and 2 patients experienced a decrease in platelet (PLT) and white blood cell (WBC) counts, respectively. These patients were among the 4 patients who were exposed to chemotherapy (Table 1). None of the nonexposed 4 patients developed bone marrow toxicity at the 6-week interval (Table 1).

DISCUSSION

Sr-89 has a palliative role in the treatment of bone metastases. Robinson et al[16] reported 137 patients treated with 1.11–1.48 Mbq/kg Sr-89 of whom 80% were improved. Other studies reported similar results,[7,10] whether it was given once or in repeated doses. The benefit was attributed to the radioactive isotope rather than to the stable strontium.[17] A better response rate was observed in patients with high performance status,[18] even if the painful lesions were exposed to previous radiotherapy.[19] Encouraging results were reported in using both chemotherapy and Sr-89.[20,21] The scheduling of either repeated doses of Sr-89 or for the duration of chemotherapy was 3 to 6 months and 6 weeks to 3 months, respectively, and it was partly based on the assumption of Sr-89 Te. The ways Sr-89 Te was determined were based on either bremsstrahlung scans or by using Sr-85. Both ways have inherent faults and cannot be routinely done in PCP.

In this study, we were able to monitor blood and urine levels of both Sr-89 and Sr-85 in a relatively convenient and accurate way. We found that Sr-85, available in Metastron in a very low dose, produced gamma emission that could not only be highly detected by an HPGe detector but even better than the corresponding Sr-89 gamma emission. We could then calculate the Sr-85 Tb and, subsequently, the Sr-89 Te: 5 times the Te is the time interval that may leave 5% of Sr-89 in the body and this time interval probably serves to fix the timing for chemotherapy delivery or for repeated doses of Sr-89. The time it takes for bone marrow depression, which may occur 4 to 6 weeks after Sr-89 treatment, is another way for scheduling retreatment. This timeframe is not recommended, however, when Sr-89 is combined with

TABLE 3. Sr-85 and Sr-89 Urine Levels in Patients With Prostate Cancer Treated With Metastron

Patient	Time Postinjection (days)	Sr-85 Activity (μCi/mL)	Sr-89 aAtivity (μCi/mL)
1	21	6.04×10^{-6}	$<$(MDA = 1.8×10^{-3})
	73	$1{,}04 \times 10^{-6}$	$<$(MDA = 2.2×10^{-3})
2	24	2.81×10^{-6}	$<$(MDA = 8.2×10^{-3})
	80	3.08×10^{-7}	$<$(MDA = 6.8×10^{-3})
3	49	4.37×10^{-6}	$<$(MDA = 1.12×10^{-3})
	77	3.31×10^{-7}	$<$(MDA = 3.59×10^{-4})
	148	1.57×10^{-7}	1.12×10^{-4}
	160	$<$(MDA = 1.57×10^{-7})	$<$(MDA = 1.12×10^{-4})
4	21	4.87×10^{-6}	$<$(MDA = 1.8×10^{-3})
	49	1.47×10^{-6}	$<$(MDA = 1.8×10^{-3})
	77	1.11×10^{-6}	$<$(MDA = 1.8×10^{-3})
	91	4.54×10^{-7}	$<$(MDA = 1.8×10^{-3})
5	35	5.60×10^{-7}	$<$(MDA = 1.4×10^{-3})
	49	4.95×10^{-7}	$<$(MDA = 1.8×10^{-3})
	84	$<$(MDA = 2.0×10^{-7})	$<$(MDA = 1.8×10^{-3})
	98	9.80×10^{-8}	$<$(MDA = 1.1×10^{-3})
6	21	3.06×10^{-6}	$<$(MDA = 1.8×10^{-3})
	49	6.58×10^{-7}	$<$(MDA = 1.12×10^{-3})
	78	1.15×10^{-7}	$<$(MDA = 1.8×10^{-3})
	112	$<$(MDA = 1.15×10^{-7})	$<$(MDA = 1.12×10^{-3})
7	20	2.47×10^{-6}	$<$(MDA = 1.8×10^{-3})
	49	4.58×10^{-7}	$<1.12 \times 10^{-3}$
8	27	1.21×10^{-6}	1.41×10^{-3}
	34	8.8×10^{-7}	$<1.8 \times 10^{-3}$
	129	$<$(MDA = 7.1×10^{-8})	$<1.1 \times 10^{-3}$

chemotherapy because the chemotherapy itself may induce bone marrow toxicity. In our current study, 3 of 4 patients who were exposed to chemotherapy did develop bone marrow toxicity at 6 weeks after Sr-89 treatment, but none of the nonchemotherapy-treated patients did so (Table 1).

TABLE 4. Calculated Tb and Te of Sr-85 and Sr-89

Patient No.	Sr-85 Tp	Sr-85 Tb	Sr-85 Te	Sr-89 Tp	Sr-89 Te
1	64.85	28.92	20.00	50.5	18.6
2	64.85	31.06	21.00	50.5	19.2
3	64.85	35.04	23	50.5	20.7
4	64.85	16.10	12.90	50.5	12.2
5	64.85	11.82	10.00	50.5	9.6
6	64.85	15.87	12.75	50.5	12.1
7	64.85	14.28	11.70	50.5	11.1

Tp, physical half-life; Tb, biologic half-life; Te, effective half-life.

We also found that there is a wide difference in the Te between patients. This supports our policy that the schedule for treatment is better based on individual Sr-89 kinetics rather than being fixed at 6 weeks to 3 months (for concurrent chemotherapy) or 3 to 6 months (for repeated Sr-89 treatment). The device used for this study, an HPGE detector, is a basic inexpensive one that is available in an ordinary nuclear facility research unit. It might be modified for better clinical suitability and for a wider range of clinical indications (such as monitoring radiolabeled monoclonal antibody levels).

In conclusion, Sr-89 Te can be individually calculated based on Sr-85 urine levels measured by an HPGe detector. The individually calculated Te can then determine the schedule for repeated Sr-89 doses and for the duration of chemotherapy delivery.

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