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¹³¹I-Tositumomab Myeloablative Radioimmunotherapy for Non-Hodgkin Lymphoma: Radiation Dose to Testes

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Abstract

Purpose—To investigate radiation dose to testes delivered by radiolabeled anti-CD20 antibody and its effects on male sex hormone levels.

METHODS—Testicular uptake and retention of ¹³¹I tositumomab were measured and testicular absorbed doses were calculated for 67 male patients (54 ± 11 years old) with non-Hodgkin lymphoma who underwent myeloablative radioimmunotherapy (RIT) using ¹³¹I-tositumomab. Time-activity curves for the major organs, testes, and whole body were generated from planar imaging. In a subset of patients, male sex hormones were measured before and one year after the therapy.

RESULTS—Absorbed dose to testes showed considerable variability (range = 4.4 to 70.2 Gy). Pre-therapy levels of total testosterone were below the lower limit of the reference range, and post-therapy evaluation demonstrated further reduction (4.6 ± 1.8 nmol/L (pre-RIT) vs. 3.8 ± 2.9 nmol/L (post-RIT), p < 0.05). Patients receiving higher radiation doses to the testes (> 25 Gy) showed a greater reduction (4.7 ± 1.6 nmol/L (pre RIT) vs. 3.3 ± 2.7 nmol/L (post-RIT), p < 0.05) than did patients receiving lower doses (< 25 Gy), who showed no significant change in total testosterone levels.

CONCLUSION—The testicular radiation absorbed dose varied highly among individual patients. Patients receiving higher doses to testes were more likely to show post-RIT suppression of testosterone levels.

Keywords

¹³¹I-tositumomab; follicular lymphoma; radioimmunotherapy; radiation dosimetry; male sex hormones

INTRODUCTION

Radiolabeled anti-CD20 antibodies represent a promising new therapeutic approach for patients with relapsed B-cell lymphoma [1]. In particular, high-dose radioimmunotherapy (RIT) can deliver potentially curative doses of radiation to tumor sites while limiting the

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relative radiation exposure to non-target organs [2]. Although previous studies have investigated the total absorbed dose and biological effects of high-dose RIT on the critical organs such as liver and lungs [3, 4], little is known of the effects of high-dose therapy on non-critical organs. For male patients, testicular exposure from high-dose RIT is of concern as it may lead to decreased serum testosterone levels, potentially affecting fertility and quality of life after treatment. As reported previously, male lymphoma survivors often suffer from poor sexual function [5]. The physiological mechanism of sexual dysfunction is thought to be multifactorial; however, a close link exists between male sex hormonal changes and sexual function [6]. Until now, we know of only limited data on radiation absorbed dose to the testes and its effects on serum testosterone level associated with high-dose RIT. The purpose of this study was to evaluate radiation absorbed dose to testes from high-dose ^{131}I -tositumomab RIT and to investigate its effects on gonadal function as reflected in male sex hormone levels.

METHODS

Study Subjects

We retrospectively reviewed the radiation absorbed dose estimates for 67 consecutive male patients (mean age 54 ± 11 years, ranging from 32 to 76 years old at the time of radiation treatment) with B-cell non-Hodgkin lymphoma (NHL) who underwent myeloablative therapy with high-dose ^{131}I -tositumomab RIT at the University of Washington Medical Center between July 2002 and April 2008. Entry criteria for the treatment protocol required patients to have tumors expressing CD20 antigen, an Eastern Cooperative Oncology Group performance status score of 0 or 1, normal renal and liver function, and no more than 25% cancer involvement of the bone marrow. The treatment was performed with the approval of the human subjects and radiation safety committees at the University of Washington, Seattle. Informed consent was obtained from all patients, and all patients enrolled in the study met protocol requirements.

Sex Hormone Measurements

Using commercially available immunological techniques, serum levels of sex hormones—total testosterone, follicular stimulating hormone (FSH), and luteinizing hormone (LH)—were measured pre-RIT therapy. One-year post-RIT hormone measurements were done in a subgroup of patients who were available for follow-up. Among 67 patients involved in the study protocol, one-year post therapy total testosterone data were successfully collected in 21 patients, FSH data in 17 patients, and LH data in 19 patients.

Radioimmunoconjugate

For the 38 patients treated before October 2006, radioiodination of murine monoclonal anti-CD20 antibody (tositumomab immunoglobulin G2a [IgG2a]; GSK Inc., Philadelphia, PA) was performed at the radiochemistry facility of the Division of Nuclear Medicine at the University of Washington using the chloramine-T labeling method [7–9]. For the 29 patients treated October 2006 and after, radioiodinated tositumomab was obtained from a commercial source (GSK Inc., Philadelphia, PA).

Biodistribution Studies for Treatment Planning

For each patient, a trace amount of ^{131}I -tositumomab was administered as part of a pre-therapy biodistribution study to determine uptake of the radioimmunoconjugate, retention, and clearance in and from the major organs and tissues and to evaluate organ-specific radiation doses from RIT. The tracer infusion (185–370 MBq, or 5–10 mCi) of ^{131}I -tositumomab antibody (1.7 mg/kg) was administered intravenously after dilution to

approximately 30 mL with normal saline. Serial anterior and posterior gamma camera images of the chest, abdomen, and pelvis were obtained immediately after tracer-level ^{131}I -antibody administration, and again approximately 48, 96, and 120 hours after tracer infusion [8] using a Maxxus dual-head camera with a dedicated Starcam computer (General Electric, Waukesha, WI), a high-energy collimator, and a 20% window centered on the 364 keV peak of ^{131}I . Counts were corrected for background radioactivity and photon attenuation using a region of interest (ROI) drawn over the peripheral soft tissue. To correct for physical decay at each time point immediately following completion of patient imaging, we imaged a flask containing a known quantity of ^{131}I in water. A region of interest drawn around the flask allowed calculation of a conversion factor relating counts detected by the camera to activity present in the flask. This conversion factor was used to calibrate patient counts detected by the camera to activity remaining in the patient at each time point.

Whole-body activity was measured at the same time points using a shielded detection probe interfaced with a multichannel analyzer (Ludlum Model 261; Ludlum Measurements Inc, Sweetwater, TX). Anterior and posterior whole-body counts were obtained by directing the probe toward the standing patient from a five-meter distance, thus capturing counts from the full height and width of the patient. The geometric mean of the anterior and posterior whole-body counts was used to calculate whole-body retention. Counts were corrected for physical decay using an ^{131}I standard.

Imaging Measurements

Uptake of the radioimmunoconjugate in the testes was determined by drawing testicular ROIs derived from tracer-level ^{131}I -tositumomab images of the pelvis (anterior projection only) and serially measuring ^{131}I counts (Fig. 1). Planar images of the pelvis were acquired with each patient's scrotum as close as possible to the anterior detector, with the penis positioned such that it was not overlying the testes. For each patient, the testicular ROI was hand-drawn by an experienced nuclear medicine technologist using the ^{131}I -tositumomab image with the best testes-to-background ratio—usually the 120-hour post-infusion image—with thigh used for the background ROI. This region was then applied to all anterior pelvis images. Because of the anterior, superficial location of testes, we did not perform attenuation correction. The standard MIRD adult testes mass (39.1 g) was used in the dose calculation for this organ [10].

Measurements of serial uptake in lungs, liver, spleen, kidneys, thyroid, and bladder (if imageable) were generated using techniques described elsewhere [4]. After measurement data were obtained for all time points, we applied a first- or second-order exponential or other appropriate mathematical function and obtained a best-fit equation (time-activity curve) by least-squares linear regression using commercially available mathematic software (CurveExpert ver. 1.4, Daniel Hyams; TableCurve 2D ver. 5.01, Systat Software, Inc.). We integrated the time-activity curves for each lymphoma patient to determine the testes residence time. We also evaluated the residence times for other major organs and remainder of the whole body to calculate the organ doses. For this study during the period 2002–2008, we used the S-values (mean absorbed dose per unit cumulated activity) available in MIRDOSE2 (Stabin, MG; Oak Ridge Associated Universities, Oak Ridge, TN), which implements the MIRD schema.

Treatment Dose

The ^{131}I activity appropriate for treating each patient's lymphoma was determined by calculating the amount of ^{131}I that would deliver a fixed maximum radiation absorbed dose to whichever critical normal organ would be receiving the highest dose. Normal organ absorbed dose was calculated using residence times obtained from planar imaging with

standard mathematical methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine [10]. For patients under 60 years of age, the maximum normal organ therapy dose was set at 27 Gy; for patients 60 years and older, the maximum normal organ dose was set at 25 Gy [7].

Statistical Analysis

Pre- and post-therapeutic serum levels of total testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) were investigated using the Wilcoxon signed rank test. Data are presented as mean $\pm$ s.d; p-values less than 0.05 were considered statistically significant.

RESULTS

Iodine-131-Tositumomab Biokinetics in the Testes

Figure 2 shows the decay-corrected (biological) uptake and retention of ^{131}I -tositumomab in the testes for one patient (WBH). The data shown for patient WBH were fitted to a two-exponential function of the form $y = a \exp(-bx) - c \exp(-dx)$; this curve is typical of other time-activity curves for the patient population ($n=67$). In Figure 2, the long-term biological retention half-time is 375 h. We integrated the area-under-curve for this function (numerically equal to $a/b + c/d$) to determine the testicular residence time, a value used in the MIRD schema, to calculate the testicular absorbed dose for this patient (Fig. 2).

Figure 3 shows the distribution of measurement values representing the fractional uptake of ^{131}I -tositumomab in the testes over time (decay-corrected), plotted collectively for 67 lymphoma patients. The broad distribution of measurements shows the high degree of variability among patients in testicular uptake. The mean initial uptake at $t = 0$ hours was 0.234 percent (± 0.132 percent) of the administered activity. Least-squares regression analysis on a single-exponential function fit to these pooled data indicated a mean retention half-time of 367 h (Fig. 3).

Dosimetry

The mean testicular absorbed dose per unit administered activity for the entire study population ($n = 67$) was 1.18 ± 0.59 mGy/MBq (range = 0.29 to 3.20 mGy/MBq). With a mean ^{131}I -tositumomab therapeutic administered activity of 21.8 ± 6.7 GBq (range = 9.3 to 50.8 GBq), mean total therapy radiation dose to the testes was 25.4 ± 14.6 Gy. Testicular absorbed dose showed considerable variation (range = 4.4 to 70.2 Gy). A histogram of testicular doses showed a median value of 22.0 Gy with a coefficient of variation of 0.58. Twenty-eight of the 67 patients (42%) received a testicular dose ≥ 25 Gy (Fig. 4).

I-131 tositumomab Radioimmunotherapy Effects on Hormone Levels

In the subset of patients in whom post-RIT serum sex hormone levels were obtained, comparison of pre- vs. post-RIT serum sex hormone levels showed that mean pre-therapy levels of total testosterone (4.6 ± 1.8 nmol/L) were lower than the lower limit of the reference range (lower limit of normal reference range for total testosterone = 10.4 nmol/L). The mean pre-therapy level of FSH (19.5 ± 8.3 IU/L) was higher than the upper limit of the reference range (reference range for FSH = 1.5–12.4 IU/L), while the mean pre-therapy level of LH (7.1 ± 4.0 IU/L) was within the normal reference range (reference range for LH = 1.7–8.6 IU/L). Follow-up evaluation one year post-RIT demonstrated a significant reduction in mean total testosterone (reduction to 3.8 ± 2.9 nmol/L, a decrease of 17.4 %, $p < 0.05$ vs. pre-RIT). In particular, patients receiving a radiation dose to the testes of ≥ 25 Gy showed a significant ($p < 0.05$) 29.8% reduction in mean total testosterone— 4.7 ± 1.6 (pre-RIT) vs. 3.3 ± 2.7 (post-RIT) nmol/L—while patients receiving a radiation dose to the testes

< 25 Gy showed a non-significant ($p = 0.75$) 7.0% reduction— 4.6 ± 2.0 (pre-RIT) vs. 4.3 ± 3.1 (post-RIT) nmol/L (Table 2). Similarly, mean serum FSH levels increased significantly ($p < 0.05$) from pre-RIT to post-RIT in patients who received testicular doses ≥ 25 Gy, increasing from 17.4 ± 5.4 IU/L to 30.7 ± 11.9 IU/L, while FSH levels in patients who received testicular dose < 25 Gy showed a non-significant ($p = 0.125$) increase from 22.4 ± 11.0 to 37.1 ± 11.4 IU/L. Serum LH levels trended toward an increase, but did not reach statistical significance for either subgroup of patients (Fig. 5).

DISCUSSION

Cancer therapies frequently produce side effects that affect the gonads. Because of this, sex hormones have been investigated as markers of gonadal side effects incurred from various cancer therapies [11–13]. For external beam radiation, even if the testes are not in the therapeutic field or are in the field but shielded, radiation scattered from adjacent fields to the testes has been shown to suppress testicular function, as evidenced by consistently elevated serum FSH levels. LH levels, in contrast, may be either increased [12] or unchanged [11]. In agreement with studies looking at other cancer therapies, we found significant post-therapy changes in male sex hormone levels in some patients receiving RIT. Specifically, we found significant post-therapy reductions in serum total testosterone, significant post-therapy increases in FSH, and a trend toward increases in LH in those patients receiving the highest testicular radiation exposure from RIT. This finding suggests a significant hormonal effect from higher ^{131}I radiation doses.

In the present study, mean testicular absorbed dose per unit of activity, estimated from dosimetry based on the standard MIRD model, was 1.18 ± 0.59 mGy/MBq administered (range = 0.29 to 3.20). The variability in testicular absorbed dose could be discussed from both technical and biological aspects. Regarding technical uncertainties in testicular dose assessment, the primary source of measurement uncertainty in testicular dose assessment is the anterior-view planar imaging, especially in light of low testicular uptake observed in many patients, scrotal positioning, and potentially variable distances between target organ and detector head. A second source of measurement uncertainty may be region-of-interest determination, which could lead to greater variation in activity determination compared to larger organs (such as liver) with higher immunoconjugate uptakes. These measurement uncertainties can be minimized by operator experience and measurement consistencies from one patient to the next. Lastly, the variation in actual testicle mass (not measured) relative to standard man models represents an additional source of uncertainty in dose assessment. We did not quantify the uncertainties, but typical experience shows variation of 10 to 20 percent, which may not be significant considering the natural biological variation in testicular uptake and retention of the radioimmunoconjugate from one patient to another. Biologically, the high degree of variability in testicular absorbed dose is unlikely to be attributable to a size effect on clearance time; since testicular volume is relatively small compared to that of other organs (reported mean for adult human = 18 cm^3 per testis, range = 12 to 30) [14] the size effect on clearance time was considered to be smaller compared to that of larger organs. Variation in testicular radiation absorbed dose may be attributable at least in part to testicular circulation, as testicular circulation is known to be controlled by sex hormones [15, 16], particularly by testosterone [17].

Forty-two percent of our patients received a radiation absorbed dose to the testes ≥ 25 Gy, which is considered the upper limit of the radiation dose for the treatment of testicular leukemic relapse that will still minimize side effects [18]. This result represented a much higher radiation dose to the testes than that typically incurred by thyroid cancer patients receiving radioactive iodine (0.75 – 1 Gy) [19] or prostate cancer patients receiving scattered radiation from external beam therapy (1.84 – 2.42 Gy) [20]. Studies on thyroid

cancer patients have reported transient gonadal radiation effects after administration of radioactive iodine. Although biochemical abnormalities generally resolved within 18 months, these studies showed that persistently abnormal serum sex hormone levels may follow from ^{131}I -induced testicular irradiation in excess of 20 Gy [21]. Our study suggests that male patients receiving higher testicular radiation doses from ^{131}I -tositumomab RIT may be at increased risk for infertility and abnormalities of hormonally-mediated sexual dysfunction [5]. Since fertility is an important issue for cancer patients, fertility preservation options should be considered for young adults receiving high-dose ^{131}I -tositumomab RIT. In the adolescent and adult male, cryopreservation of semen is a safe and effective way of preserving fertility when the treatment results in permanent sterility [22].

To our knowledge, the total absorbed dose to the testes and the relationship between dose and serum sex hormone levels in high dose RIT using ^{131}I -tositumomab has not been previously reported. Testicular dosimetry has been reported, however, for RIT using a different radiolabeled monoclonal antibody, ^{90}Y -ibritumomab [23]. In the present study, the range of absorbed doses to the testes per unit administered activity using ^{131}I -tositumomab (0.29 – 3.20) is slightly lower than that reported with ^{90}Y -ibritumomab (1.3 – 4.7) [23–25]. However, overall testicular radiation dose is higher with ^{131}I -tositumomab compared to ^{90}Y -ibritumomab due to much higher activity levels of ^{131}I given to the patients with ^{131}I -tositumomab (range 9.3 – 50.8 GBq) compared to ^{90}Y -ibritumomab (range 1.85 – 5.55 GBq). Although previous studies found no significant radiation effects from RIT with ^{90}Y -ibritumomab, the higher testicular radiation doses given in the present treatment protocol utilizing ^{131}I -tositumomab may increase the risk of testicular hypofunction.

The present study has several limitations. First, we looked only at differences in serum hormone levels, not at fertility, sexual functioning, or other changes that might follow from altered hormone levels. These other factors were not assessed in this study, and their absence may limit the interpretation of the significance of the measured hormonal changes. Utilizing a questionnaire, Caffo et al. investigated changes in sexual functioning in seminoma patients undergoing orchidectomy followed by radiotherapy. They found that, after treatment, 24% of patients reported a low semen volume, 14% premature ejaculation, 2% late ejaculation, and 2% an absence of ejaculation (median follow-up of 123 months, range = 15 to 496 months) [26]. Further investigations in our study should include correlation of testicular radiation exposure and hormonal changes with semen analysis and sexual functioning.

Second, because the present study was limited to male patients whose NHL had relapsed, all patients enrolling had already undergone chemotherapy prior to the high-dose RIT. Thus what we measured as pre-RIT serum sex hormone levels also represented post-chemotherapy serum sex hormone levels, likely reflecting on some level the effects of prior treatment rather than presenting as a naïve physiological state. We did not control for differences in chemotherapeutic regimens for patients enrolling in this study, such as the specific chemotherapeutic drugs involved, drug doses, number of rounds of chemotherapy, or time interval between finishing chemotherapy and enrolling in this study. These differences have the potential not only to affect pre-RIT gonadal hormone levels but also how testicular radiation absorbed dose changes gonadal hormone levels.

Third, post-RIT hormone measurements were done not on the entire study group of 67, but rather in a subgroup of patients (total testosterone in 21 patients, FSH in 17, LH in 19) available for one-year follow-up. There is the possibility of introduction of an inadvertent selection bias related to factors affecting availability for follow-up. No such bias is known to be present, but the possibility exists.

Finally, age may influence gonadal hormone levels. The present study population included 19 patients over 60 years old at the time of initial RIT. Although serum sex hormone levels may vary with age, this study focused on one-year pre- to post-RIT changes. This one-year interval is short enough that age-related changes in gonadal hormone levels would not be expected to be a major contributor to pre- to post-RIT changes.

Patients receiving higher testicular radiation exposure from ^{131}I -tositumomab RIT appear to experience suppressed serum testosterone levels; however, higher testicular radiation exposure may have the potential for a positive treatment effect as well. Testicular relapse, seen in both primary and secondary lymphomas, is a well-recognized phenomenon, accounting for 5% of all testicular malignancies and 1% of all lymphomas. Although it is the most common testicular malignancy in patients older than 60 years of age [27], testicular infiltration may not be clinically detectable. An autopsy study examining 124 male lymphoma patients found eleven (8.9%) with testicular involvement, only two of which were known prior to autopsy [28]. A higher testicular radiation absorbed dose may theoretically provide an advantage in treating NHL patients with a highly aggressive histology, in whom the testes may be sanctuary sites for lymphoma.

CONCLUSIONS

Testicular radiation absorbed doses in high-dose ^{131}I -tositumomab RIT demonstrated individual variation, and were higher than doses previously reported from RIT with ^{90}Y -ibritumomab, from radioiodine for thyroid cancer, or from scattered radiation from external beam treatment for prostate cancer. Patients who received a radiation dose of equal to or greater than 25 Gy were more likely to show a significant decrease from baseline in serum gonadal hormone levels one year after treatment compared to patients who received a radiation dose of less than 25 Gy. A higher testicular radiation absorbed dose may theoretically provide a therapeutic advantage in patients who have microscopic or clinical disease with a highly aggressive histology, in whom the testes may be sanctuary sites for lymphoma.

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^{131}I -Tositumomab

Day 0

Day 6

Testis ROI using ^{131}I -Tositumomab

Figure 1. Representative images of whole body ^{131}I -tositumomab on post-infusion days zero and six (a), and testicular ROIs placed on an anterior planar image of ^{131}I -tositumomab (b).

Figure 2.

Plot of the fraction administered ¹³¹I activity accumulating in testes over time, corrected for decay, for a typical patient (WBH) in the study. We fit the measurement data to a bi-exponential equation using least-squares regression analysis, and integrated the area-under-curve for calculating testicular absorbed dose.

Figure 3.

Plot of the pooled measurement data for 67 lymphoma patients representing fraction of administered ^{131}I activity in the testes, corrected for decay. This single-exponential plot provides the mean fraction of the administered activity localizing in the testes at $t = 0$ (0.234 percent) and the mean retention half-time (367 h) for these patients.

Testes

Whole Body

Figure 4.
Histogram of radiation absorbed dose of testes for the entire study population (n = 67).

Figure 5.

Serum sex hormone levels pre- (open column) vs. post- (solid column) RIT. Total = all patients with hormonal data; high = patients receiving testicular radiation absorbed dose 25 Gy; low = patients receiving testicular radiation absorbed dose < 25 Gy.

TABLE 1

Organ Absorbed Doses For The Entire Study Population (n=67)

	Absorbed dose per unit administered activity in mGy/MBq (mean $\pm$ s.d.)	Estimated total cumulative absorbed radiation dose in Gy (mean $\pm$ s.d., range)
Whole Body	0.22 $\pm$ 0.05	4.4 $\pm$ 0.8 (2.4 – 6.7)
Liver	1.03 $\pm$ 0.29	21.4 $\pm$ 4.8 (6.5 – 27.2)
Lungs	1.19 $\pm$ 0.50	23.3 $\pm$ 3.7 (9.5 – 28.4)
Spleen	1.51 $\pm$ 1.07	31.6 $\pm$ 27.6 (4.0 – 233.4)
Testes	1.18 $\pm$ 0.59	25.4 $\pm$ 14.6 (4.4 – 70.2)

TALBE 2**Comparison of hormone levels Pre vs. Post RIT**

Radiation to testes 25 Gy				
	n	Pre RIT	Post RIT	P-value
Total testosterone (nmol/L)	11	4.7 ± 1.6	3.3 ± 2.7	0.0117
FSH (IU/L)	11	17.4 ± 5.4	30.7 ± 11.9	0.0215
LH (IU/L)	12	7.0 ± 4.2	10.5 ± 5.1	0.3877
Radiation to testes < 25 Gy				
	n	Pre RIT	Post RIT	P-value
Total testosterone (nmol/L)	12	4.6 ± 2.0	4.3 ± 3.1	0.7539
FSH (IU/L)	8	22.4 ± 11.0	37.1 ± 11.4	0.125
LH (IU/L)	7	7.1 ± 4.1	14.6 ± 9.3	0.4531
All patients				
	n	Pre RIT	Post RIT	P-value
Total testosterone (nmol/L)	23	4.6 ± 1.8	3.8 ± 2.9	0.0266
FSH (IU/L)	19	19.5 ± 8.3	33.4 ± 11.8	0.023
LH (IU/L)	19	7.1 ± 4.0	12.0 ± 7.0	0.1671

RIT = Radioimmunotherapy

FSH = Follicle-Stimulating Hormone

LH = Luteinizing Hormone