Observational Retrospective Study of Altered Biodistribution of Tositumomab and ^{131}I-Tositumomab

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The tositumomab/^{131}I-tositumomab radioimmunotherapy regimen is administered as a dosimetric dose followed by a therapeutic dose. The biodistribution of the dosimetric dose is assessed by quantitative calculations of whole-body residence time (TBRT) and visual examination of whole-body γ-camera images, to determine the administered radioactivity dose and whether a therapeutic dose can be administered. We investigated whether altered biodistribution of ^{131}I-tositumomab could be identified using quantitative TBRT. **Methods:** BioClinica, Inc., provided γ-camera images to an independent reviewer to assess altered ^{131}I-tositumomab biodistribution in patients reported to a registry. **Results:** Of 2,649 therapeutic doses, 5 (0.2%) were cancelled because of altered biodistribution as determined by γ-camera images and TBRT. Of these, 3 γ-camera images were assessed by the independent reviewer; one showed altered biodistribution (0.04%) and was in agreement with the TBRT on-site calculation. **Conclusion:** TBRT alone should be used to determine altered biodistribution and hence whether to administer the therapeutic dose.

Key Words: tositumomab; altered biodistribution; therapeutic dose

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Tositumomab/^{131}I-tositumomab (TST/^{131}I-TST [Bexxar]; GlaxoSmithKline) is an anti-CD20 antibody regimen and was approved in the United States in 2003 for the treatment of patients with rituximab-refractory, CD20-positive, low-grade non-Hodgkin lymphoma with or without transformation (*1–4*). The TST/^{131}I-TST regimen consists of a 2-part dosimetric step, followed 7–14 d later by a 2-part therapeutic step (*1*). Whole-body clearance is patient-specific, and high doses of ^{131}I-TST are known to cause myelosuppression, nausea, infections, and cardiotoxicity (*5*). Therefore, ^{131}I-TST biodistribution is assessed after the dosimetric dose to determine the therapeutic dose to be given; if the biodistribution of the dosimetric dose is abnormal, the therapeutic dose is not administered. Normal biodistribution occurs in the heart and major blood vessels and, to a lesser extent, in the liver and spleen, with possible uptake in the thyroid, kidney, and urinary bladder (*1*).

Biodistribution of TST/^{131}I-TST after the dosimetric dose is assessed both by quantitative determination of whole-body residence time (TBRT) and by visual examination of whole-body γ-camera images at 3 time points. However, the necessity of acquiring more than one γ-camera image to assess biodistribution before administration of radioimmunotherapy has been questioned by data from the Zevalin Imaging Registry (*6*). These data demonstrated that a single γ-camera image obtained within 24 h of administration of the test dose of ^{111}In-ibritumomab tiuxetan successfully identified all cases of altered biodistribution (*6*).

We performed an observational, retrospective study to determine the frequency of patients with an altered biodistribution of ^{131}I-TST after receiving the dosimetric dose of TST/^{131}I-TST in the postmarketing setting. In addition, we wanted to evaluate the clinical benefit of visually assessing γ-camera images obtained after the dosimetric dose to determine the biodistribution of ^{131}I-TST and hence whether to administer the therapeutic dose.

MATERIALS AND METHODS

Study Design

This was an observational, retrospective study (GlaxoSmithKline study BEX114606) with anonymized data from patients who received the dosimetric dose of TST/^{131}I-TST in the commercial setting between June 2003 and February 2010. Commercial orders for TST/^{131}I-TST were retrospectively assessed to determine the total number of patients who received the dosimetric dose, the reasons for cancellation of the therapeutic dose, and the frequency of patients with a reported altered biodistribution. The frequency of cancellations was summarized according to medical reasons or other reasons. Whole-body γ-camera images and dosimetry calculations of the TBRT of patients who did not receive the therapeutic dose because of altered biodistribution were evaluated by an independent nuclear medicine physician. Images from patients with an expected biodistribution were not independently reviewed.

TST/^{131}I-TST was administered according to its prescribing information (*1*). The dosimetric dose consisted of 450 mg of unlabeled TST (in 50 mL of 0.9% NaCl solution) administered intravenously over 1 h, followed immediately by 35 mg of TST labeled with 185 ± 18.5 MBq (5 ± 0.5 mCi) of ^{131}I (in 30 mL of 0.9% NaCl solution) administered intravenously over 20 min. The therapeutic dose consisted of the same unlabeled TST dose, followed by 35 mg of TST labeled with a patient-specific activity of ^{131}I (in 30 mL of 0.9% NaCl solution). The required activity of ^{131}I to deliver the desired whole-body dose of radiation was calculated according to the patient platelet count: 65 cGy if the platelet count was 100,000–149,999/mm^3; 75 cGy if the platelet count was at least 150,000/mm^3 (*1*).

Assessment of Dosimetry and Biodistribution

After the dosimetric dose, whole-body γ-camera counts and whole-body γ-camera images were obtained at 3 time points: within 1 h of infusion and before urination, 2–4 d after infusion of the dosimetric dose, and 6–7 d after infusion of the dosimetric dose. TBRT was the

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time in hours at which the activity was 37% of that at time zero; the activity was measured by whole-body γ-camera counts.

Data Collection and Management

Records of completed and cancelled TST/^{131}I-TST commercial orders were maintained by the GlaxoSmithKline Speciality Service Centre using the Bexxar Operations and Order Tracking System. Reasons for cancellation of the therapeutic dose were prospectively recorded by the GlaxoSmithKline Speciality Service Centre at the time of cancellation and retrospectively confirmed by the treatment site investigator. GlaxoSmithKline used anonymized dosimetry calculations and γ-camera images from the medical centers to assess the dosimetry and biodistribution for reported cases of altered ^{131}I-TST biodistribution.

BioClinica, Inc., managed the image files and coordinated the independent review of biodistribution.

Independent Review of γ-Camera Images and Time Calculations

Whole-body γ-camera images were independently reviewed by a nuclear medicine physician who did not know the results of the original biodistribution assessment performed at the treatment sites and did not receive patient dosimetry data. The independent reviewer prepared a description of the ^{131}I-TST biodistribution at each of the 3 time points examined for each subject and, on the basis of criteria in the prescribing information (Table 1) (*1*), determined whether the ^{131}I-TST biodistribution was expected or altered.

The TBRT of ^{131}I-TST after administration of the dosimetric dose was validated by an independent reviewer in patients deemed to have an altered biodistribution. An altered biodistribution was defined as a TBRT of less than 50 h or more than 150 h (*1*).

RESULTS

Treatment Information

In total, 2,649 patients received a dosimetric dose of TST/^{131}I-TST in the postmarketing setting between June 2003 and February 2010, of whom 2,541 (96%) also received a therapeutic dose. Of the remaining 108 patients, 105 (4%) had their therapeutic dose cancelled and 3 (0.1%) were rescheduled. One patient rescheduled the therapeutic dose because of a medical condition (shingles). Medical reasons for cancellation included patient illness (n = 47, 1.8%), adverse event during or after the dosimetric dose (n = 12, 0.5%), low platelet count (n = 10, 0.4%), unrelated medical conditions (n = 8, 0.3%), altered biodistribution (n = 5, 0.2%), and death (n = 2, 0.1%). One death was caused by disease progression and the other by an anaphylactic reaction. Nonmedical reasons for cancellation were logistics (n = 11, 0.4%), patient compliance with radiation safety (n = 5, 0.2%), the physician's decision (n = 4, 0.2%), and the patient's decision (n = 1, 0.04%).

Altered Biodistribution Reported by the Treatment Sites

In total, 5 patients (0.2%) who received the dosimetric dose of TST/^{131}I-TST were determined to have altered biodistribution by the treatment site investigator because of reported lung uptake (n = 3), reported stomach uptake (n = 1), and a TBRT of 45 h (n = 1).

Independent Review of γ-Camera Images and Time Calculations

Whole-body γ-camera images were available for 3 of the 5 patients who had altered biodistribution after the dosimetric dose according to the site investigator. Descriptions of the visual assessment of γ-camera images are presented in Table 2. The independent reviewer concluded that 1 of the 3 patients had an altered biodistribution, representing 0.04% of all patients receiving the dosimetric dose.

Dosimetry calculations were performed by the treatment site investigator for 3 of the 5 patients deemed to have an altered biodistribution. The TBRTs were calculated as 45, 101, and 154 h (Table 2). These dosimetry calculations were independently assessed, and all 3 were found to be accurate. Hence, 2 patients

TABLE 1
Expected and Altered Biodistribution of ^{131}I-TST (*1*)

Biodistribution	Description
Expected	Most activity in blood pool on first* image; with uptake in normal liver and spleen less than that in heart on day of dosimetric dose
	Significantly decreased activity in blood pool during second† and third‡ images
	Decreased accumulation in normal liver and spleen during second† and third‡ images
	Possible uptake in thyroid, kidney, and urinary bladder, with minimal uptake in lungs during second* and third‡ images
	Possible increased intensity at known lymphoma sites during second* and third† images
Altered	No activity visualized in blood pool on first‡ image
	Diffuse, intense tracer uptake in liver or spleen or uptake suggestive of urinary obstruction on first‡ image
	Diffuse uptake in normal lung greater than that in blood pool on first* image
	Uptake suggestive of urinary obstruction
	Diffuse uptake in normal lung greater than that in blood pool
	TBRT $<$ 50 h or $>$ 150 h

*Image taken on day 0.
†Image taken on day 2, 3, or 4.
‡Image taken on day 6 or 7.

TABLE 2
Results of Patients Not Receiving Therapeutic Dose Because of Altered Biodistribution

Patient no.	Assessment by treatment site		Assessment by independent review	
	Biodistribution by visual inspection of γ images	TBRT (h)	Visual assessment of γ-camera images	Biodistribution result
1	Unknown*	45	Day 0: Most activity in blood pool, and uptake in normal liver and spleen less than in heart	Altered
			Day 4: Blood pool not visualized; diffuse, increased uptake in liver and spleen	
			Day 7: Altered biodistribution best appreciated by comparison of 3 image sets	
2	Altered by lung uptake	154	Day 0: Most activity in blood pool; uptake in normal liver and spleen less than in heart	Expected
			Day 2: Most activity in blood pool; uptake in normal liver and spleen less than in heart	
			Day 6: Most activity in blood pool; uptake in normal liver and spleen less than in heart; normal biodistribution best visualized on day 0	
3	Altered by lung uptake	101	Day 0: Most activity in blood pool; uptake in normal liver and spleen less than in heart	Expected
			Day 3: Most activity in blood pool; uptake in normal liver and spleen less than in heart; tumor targeting	
			Day 6: Most activity in blood pool; uptake in normal liver and spleen less than in heart; tumor targeting; normal biodistribution best visualized on day 3	
4	Altered by stomach uptake	NR	NA	—
5	Altered by lung uptake	NR	NA	—

*Deemed to have altered biodistribution because of TBRT of 45 h.
NR = not reported; NA = not available.

(0.08% of total) had a TBRT outside 50–150 h (i.e., defined as altered biodistribution).

DISCUSSION

This study suggests that patients rarely have an altered biodistribution of ^{131}I-TST when treated with TST/^{131}I-TST in the postmarketing setting (≤0.2%).

The investigators' and reviewers' assessments of altered biodistribution based on whole-body γ-camera images were conflicting; only 1 of 3 patients who were identified by investigators to have altered biodistribution by whole-body γ-camera images was confirmed to have altered biodistribution on independent review. Thus, assessments of abnormal biodistribution by whole-body γ-camera images were not reproducible. The increased lung uptake of ^{131}I-TST on early images was not verified by central review, suggesting that this criterion for altered biodistribution is not particularly reliable.

Conversely, TBRT calculated by the site investigators was confirmed by the independent reviewer and hence deemed reproducible. Furthermore, TBRT is substantially based on the same factors as blood clearance and so provides an objective, indirect method to determine biodistribution.

We believe these results demonstrate that visual assessment of images provides minimal clinical benefit compared with TBRT. Furthermore, relying on γ-camera images may bring about inaccurate visual assessments of biodistribution resulting in therapy being withheld from patients, especially if the only finding is increased tracer uptake in the lungs. Because deiodination of antibodies can occur, radiotracer accumulation in the stomach may, in some instances, be an acceptable biodistribution as well. Hence, in one case, this "altered biodistribution" might more appropriately be considered within the reference range of biodistribution values.

Admittedly, data for 2 patients are missing. However, even with a worst-case assumption that these 2 patients had an altered biodistribution, less than 0.1% of patients studied by the imaging dosimetry method would have had an altered biodistribution detectable only by γ-camera imaging.

CONCLUSION

These data indicate that true altered biodistribution of TST/^{131}I-TST is very rare and suggest that nonimaging methods, such as measuring TBRT with a probe system or abbreviated whole-body imaging approaches, may be sufficient to identify the rare occurrences of altered biodistribution and allow individualized radiation dose delivery of TST/^{131}I-TST. Such a simplification in dosimetry assessment could make radiopharmaceutical treatment administration simpler and less expensive than recording sequential γ-camera images.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. The study was funded by GlaxoSmithKline. Thierry J. Horner is an employee of GlaxoSmithKline and owns stock/stock options in the company. Thomas S. Lin was an employee of GlaxoSmithKline and owned stock/stock options in the company at the time of the study. No other potential conflict of interest relevant to this article was reported.

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