

Anaphylaxis After Administration of Ibritumomab Tiuxetan for Follicular Non-Hodgkin Lymphoma

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Abstract: We report an anaphylactic reaction in a 45-year-old gentleman with an 8-year history of extensively treated, relapsing follicular lymphoma who was receiving a second treatment with ibritumomab tiuxetan. Within seconds of receiving Y-90 ibritumomab, he developed chest tightness, shallow respirations, hypotension, and incontinence. After successful resuscitation, a human antimouse antibody (HAMA) level was found to be elevated, 618 ng/mL (reference 0–188 ng/mL).

Key Words: ibritumomab tiuxetan, anaphylaxis, murine monoclonal antibody

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Treatment of relapsed, refractory follicular lymphoma and transformed non-Hodgkin lymphoma (NHL) with the radioimmunotherapeutic agents (RIT), Y-90 ibritumomab tiuxetan (Zevalin) and I-131 tositumomab (Bexxar), has been approved by the US Food and Drug Administration.^{1,2} The package inserts for RIT warn of allergic reactions such as angioedema, acute respiratory distress, hypoxia, bronchospasm, and even anaphylactic shock with first exposure to the monoclonal antibody component of the drug. The definition of anaphylaxis includes, but is not limited to, acute onset of illness, hypotension, syncope or near syncope, and hypotonia.³ Contrary to earlier expectations, these reactions have been infrequent.^{4,5} There are a few series of cases in which responders to RIT have been re-treated. Kaminski et al⁶ describe 32 patients who, because of initial response to I-131 tositumomab, were re-treated with I-131 tositumomab. One patient experienced an anaphylactoid-type reaction associated with unlabeled tositumomab infusion during the therapeutic dose. Human antimouse antibody (HAMA) developed in 10% of in these patients. Witzig et al⁷ reported on results from a phase I study in which 15 patients received a sequen-

tial second dose of ibritumomab tiuxetan without any unexpected side effects.

We report a case of re-treatment with Y-90 ibritumomab tiuxetan associated with an anaphylactic reaction.

CASE REPORT

A 45-year-old smoker was diagnosed with follicular NHL in 1999 with extensive cervical, mediastinal, intra-abdominal, and retroperitoneal lymphadenopathy. He had an excellent response to cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) followed by adjuvant interferon. In 2002 his disease recurred with fatigue, anorexia, abdominal pressure, shortness of breath, and a left pleural effusion. He was given rituximab, ifosfamide, carboplatin, and etoposide (RICE) chemotherapy. In May 2002, he underwent autologous peripheral blood stem cell transplant and remained in remission until April 2003. Over the next several months, he progressed with extensive lymphadenopathy and a symptomatic malignant right pleural effusion.

In October 2003 he presented to our institution for evaluation of treatment with ibritumomab tiuxetan. He complained of significant dyspnea on exertion, abdominal pressure, and leg swelling. Physical examination revealed a well-developed man in no acute distress. He had palpable lymphadenopathy in his supraclavicular and right inguinal lymph node areas. He was tachycardic. Lung examination revealed dullness to percussion and decreased breath sounds over his entire right hemithorax. His abdomen was distended, nontender and without hepatosplenomegaly. There was trace edema in both lower extremities. A fusion PET-CT revealed massive confluent lymphadenopathy throughout the neck, chest, abdomen, and pelvis with markedly increased FDG uptake, as well as a massive right pleural effusion and a moderate left pleural effusion.

He was treated with additional chemotherapy consisting of fludarabine, mitoxantrone, and rituximab. Re-evaluation in January 2004 found him to be asymptomatic. He had responded partially to chemotherapy, and a follow-up fusion PET-CT showing resolution of his left pleural effusion, small residual right pleural effusion, markedly decreased lymphadenopathy, and equivocal FDG uptake. He received his first treatment with rituximab 250 mg/m² immediately followed by indium ibritumomab tiuxetan in March 2004 and a week later he received another dose of rituximab followed by yttrium ibritumomab tiuxetan without any untoward reaction.

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He remained in complete remission until July 2005 when he was noted to have an asymptomatic mass at the left lung base. He was followed expectantly and in December 2005 a fusion PET-CT revealed interval development of a large paraspinal mass extending from T6 through L1 and multiple abnormal mediastinal, retroperitoneal and mesenteric lymph nodes. Intense FDG-avidity was present in prevertebral, periaortic, retrocrural, and retroperitoneal masses. In January 2006 rituximab, 250 mg/m², followed by the imaging dose of indium-111 ibritumomab tiuxetan, 5 mCi, was administered without incident. The gamma camera scanning showed normal biodistribution. One week later he was scheduled to receive a therapeutic dose of 32 mCi Y-90 ibritumomab tiuxetan. The infusion of rituximab, 250 mg/m², given before the therapeutic dose of Y-90 ibritumomab was uneventful but after 0.5 milliliter of Y-90 ibritumomab tiuxetan, he experienced a "strange feeling," that promptly resolved. After another 0.5 milliliters was administered, he complained of dry mouth and lightheadedness, chest tightness, and shortness of breath. His breathing became shallow, and he became hypotensive (75/40 mm Hg), tachycardic, he slumped over his chair and was incontinent of urine. He was immediately given diphenhydramine 25 mg and solumedrol 100 mg intravenously, oxygen and intravenous fluids, and was transferred to the emergency room. There, he was resuscitated with additional fluid and famotidine. A blood sample was drawn for HAMA by enzyme-linked immunosorbent assay (ELISA). His level was elevated at 618 ng/mL (reference range 0-188 ng/mL). Unfortunately, a blood sample was not stored for additional evaluation, such as for human antichimeric antibody (HACA).

DISCUSSION

The use of murine and chimeric antibodies initially prompted concern for an immunologic response that would preclude re-treatment. Studies of both Y-90 ibritumomab tiuxetan and I-131 tositumomab in relapsed or refractory NHL indicated that the rate of HAMA formation in these heavily pretreated patients was low, 2% and 17%, respectively, and that they caused no clinically significant side effects.^{1,2} This low rate of HAMA may be a reflection of impaired immunity in patients with relapsed, refractory disease.² In contrast, the incidence of HAMA is reported as 63% in previously untreated patients receiving I-131 tositumomab as a single agent.⁸ There is no comparable data available on HAMA rates after first-line treatment with ibritumomab tiuxetan as a single agent. The presence after initial treatment with murine monoclonal antibody of human antiglobulin antibody (HAGA) has not been shown to be a clinical obstacle with some murine monoclonal antibodies such as Lym-1. On the contrary, there is some suggestion in the literature that there is a potential advantage of a HAMA or HAGA development after RIT. The development of polyclonal HAGA directed against epitopes on the administered antibody may generate anti-idiotypic antibody that can mimic the tumor antigen and facilitate host recognition of the tumor, and thus, may have a clinical benefit.^{4,5,9}

In the aforementioned study of 32 patients considered for re-treatment with I-131 tositumomab,⁶ 3 patients (10%) became HAMA positive and 1 patient had an anaphylactoid reaction. Our patient, upon re-treatment with Y-90 ibritumomab tiuxetan, developed anaphylaxis which to our knowledge has not been previously reported with the ibritumomab tiuxetan regimen. His case, with his acute respiratory compromise, hypotension, and incontinence meets clinical criteria for anaphylaxis.³

The anaphylactic reaction of our patient represents an immunologic response from a clonal population of "memory" B-cells. Presumably, his primary immune response occurred in 2004, with his first exposure to the dosimetric dose of indium ibritumomab tiuxetan. However, with his therapeutic dose 1 week later, he had no reaction. There is generally a lag of 5 to 7 days before antibody levels start to rise in the primary immune response.¹⁰ In a secondary immune response, the lag time before antibody levels start to rise is much shorter (1–2 days) and the levels are much higher (100- to 1000-fold higher).¹⁰ Thus, when patients are re-treated with murine and chimeric antibodies, their secondary immune response will result in more rapid antibody formation. In the patients re-treated with I-131 tositumomab, the median time to development of HAMA was 12 days.⁶ Likewise, our patient's dosimetric dose on January 26, 2006 incited a secondary immune response with amplification of a HAMA-producing population of memory B-cells which prompted his robust immunologic response to his therapeutic dose 6 days later.

The median time that HAMA antibodies remained detectable in the serum of previously untreated patients using I-131 tositumomab was 5.5 months (range 1.1–25.1).⁸ Our patient was re-treated nearly 2 years after his initial treatment with radioimmunotherapy, and he may or may not have had detectable HAMA in his serum before his dosimetric dose, but he clearly had maintained his amnestic response. Similarly, one of the tositumomab re-treated patients initially tested negative for HAMA, but then tested HAMA positive when the dosimetric dose was discontinued due to an anaphylactoid reaction.⁶ Our patient's case illustrates that even heavily pretreated patients may have a robust immune response, and it would be prudent to check HAMA levels in all patients before re-treatment with radioimmunotherapy.

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