

VIEWPOINT

HEALTH CARE REFORM

The Withdrawal of Drugs for Commercial Reasons The Incomplete Story of Tositumomab

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Drug withdrawals for commercial or financial reasons are more frequent than those for concerns about safety or efficacy, yet they attract less attention and interest. In the United States, among all new molecular entities approved from 1980 to 2009, 118 drugs were withdrawn from the market, but only 22% ($n = 26$) were withdrawn for safety reasons.¹ Among all new active substances approved in the United Kingdom between 1972 and 1994, 35 (59%) of the 59 drug withdrawals were for commercial reasons.²

In the fall of 2013, GlaxoSmithKline (GSK) withdrew its drug tositumomab (Bexxar) for marketing reasons. An anticancer radioantibody conjugate of iodine I 131, tositumomab consisted of an anti-CD20 antibody covalently linked to radioactive iodine I 131. The drug targeted cells expressing CD20 and delivered a local dose of γ - and β -radiation. Tositumomab first showed promising clinical signs in 1993 when a phase 1 trial demonstrated responses (tumor shrinkage) in patients with relapsed lymphoma.³ In 1994, the drug was granted orphan drug designation, and in 1998, the fast-track designation was added. Tositumomab was first approved by the US Food and Drug Administration (FDA) in 2003 for patients with "CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy,"⁴ according to the prescribing information. This indication was granted after a single-arm study demonstrated responses in 27 (68%) of 40 patients in this setting.⁴ In 2004, the indication was expanded to include patients who had not been treated with rituximab on the basis of a single-arm study that demonstrated a response in 28 (47%) of 60 patients.⁵ At neither the time of approval nor since has any trial shown that tositumomab improved survival for the patient groups for which it was approved.

On February 20, 2014, GSK announced that the manufacture of tositumomab would be voluntarily discontinued, citing a projected decline in sales and the availability of alternative treatments.⁶ Continued manufacture was untenable. Usage peaked in 2006, and sales decreased by 30% annually thereafter.⁶ In 2012, only 75 patients received the drug.⁶ Although no published estimates exist for the cumulative sales of the drug, a conservative estimate places annual use between 2000 and 3000 patients during the decade it was available. As tositumomab was priced at \$32 400 for a course of treatment, cumulative sales may have approached \$100 million.⁶

When tositumomab was approved, the manufacturer made a postmarketing commitment to conduct a

trial that compared the drug with rituximab among patients with relapsed follicular lymphoma. Such a trial would address the clinical question of the expanded 2004 indication. However, recruitment for this trial (clinicaltrials.gov identifier: NCT00268983) was reportedly poor. In February 2011, representatives from GSK appeared before the FDA's Oncology Drug Advisory Committee to report that the trial was unlikely to be completed and to ask that an alternative trial—one being conducted by the Southwest Oncology Group (SWOG)—be considered instead. Notably, the SWOG trial was a comparison of tositumomab and rituximab in addition to chemotherapy among patients with newly diagnosed follicular lymphoma, an indication for which tositumomab had not received approval. At the meeting, there was concern that the cooperative group study did not have standardized imaging procedures. An FDA official suggested that the trial, regardless of its result, might not be accepted by the agency. Representatives of GSK noted that no other studies were ongoing (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf>, pages 93-406).

In 2013, the SWOG trial was published and reported no benefit for tositumomab.⁷ Overall survival was worse in the tositumomab arm of the study (2-year overall survival was 93% compared with 97% for rituximab), but the difference was not significant ($P = .08$). I am aware of only 1 other randomized trial of the drug. That study enrolled patients with relapsed or persistent (but chemotherapy-sensitive) diffuse, large B-cell lymphoma and randomized them to autologous transplantation with chemotherapy and tositumomab or chemotherapy and rituximab. Overall survival was worse in the tositumomab arm (2-year overall survival of 60.1% for tositumomab vs 66.3% for rituximab), but the difference was again not significant ($P = .29$).⁸

Although tositumomab's benefits are unknown, its potential harms are clear. Tositumomab can cause severe allergic reactions at the time of infusion and prolonged and severe cytopenias.⁹ Secondary malignant neoplasms were reported in 10% of the patients enrolled in the clinical trials leading to its approval and in 3% of patients in the extended-access program.⁹ Safety concerns may have contributed to the drug's dwindling use.¹⁰

At first glance, the withdrawal of tositumomab seems unremarkable. An active, albeit challenging, drug comes to market and is voluntarily withdrawn 10 years later because sales are poor. In fact, an article summarizing the drug's history is titled "Why good drugs some-

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times fail.⁶ But the drug remains a mystery, and a final verdict will likely not be rendered. Was tositumomab a good drug that improved outcomes in specific groups of patients? All that is known is that tositumomab improved a surrogate end point in 1 population and failed to show a survival benefit in 2 other populations. As is the case for some other drugs, there are no data on whether tositumomab harmed more patients than it helped.

The decision by industry sponsors to terminate studies early for commercial reasons has been criticized; often little information emerges from these studies, and publication is infrequent. The decision to withdraw a drug for commercial reasons raises similar con-

cerns. Interest wanes in providing a firm verdict on the drug's safety and effectiveness, and information from unpublished trials becomes difficult to obtain.

With the approval by the FDA of more drugs in oncology and other specialties based on surrogate end points such as response rates, not overall survival, it is more important than ever to collect data on the ultimate efficacy of treatments. Tositumomab is a drug that many physicians outside of oncology have never heard of, but its incomplete story is a reminder of the weaknesses of our current system for approving drugs and adequately continuing to study them after approval.

ARTICLE INFORMATION

Published Online: November 10, 2014.
doi:10.1001/jamainternmed.2014.5756.

Conflict of Interest Disclosures: None reported.

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