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Evaluation of gemtuzumab ozogamycin associated sinusoidal obstructive syndrome: Findings from an academic pharmacovigilance program review and a pharmaceutical sponsored registry

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Abstract

Background—In 2000, the Food and Drug Administration (FDA) approved gemtuzumab ozogamycin for monotherapy for older patients with relapsed AML. A 0.9% rate of hepatic sinusoidal obstructive syndrome (SOS) was noted in licensing trials. In 2001, FDA received reports of 14 GO-associated SOS cases from MD Anderson Cancer Center. A State of South Carolina/National Cancer Institute funded pharmacovigilance program and a manufacturer sponsored registry independently evaluated this concern.

Methods—The manufacturer's registry and the academic program focused on risk factors and incidence of GO-associated SOS in routine clinical practice and clinical trial settings, respectively. Comparisons were made of findings and dissemination efforts from the two studies.

Results—Retrospective analysis of clinical trials by the academic initiative identified 99 cases of SOS among 221 GO-treated stem cell patients and 649 patients who did not undergo HSCTs. SOS rates were 3% when GO was administered at doses ≤6 mg/m^2 as monotherapy or with non-hepatotoxic agents; 28% when administered with 6-thioguanine, a hepatotoxic agent; 15% when administered as monotherapy at doses at a dose of 9 mg/m^2, and between 15% and 40% if a stem cell transplant (SCT) was performed within 3 months of GO administration. Death from SOS occurred in 33% of the cases. The manufacturer's registry prospectively evaluated 482 GO-treated patients who received a mean dose of 7.8 mg/m^2. Overall, 41% received concomitant chemotherapy, 18% had undergone prior SCT, 9.1% developed SOS, and death from SOS occurred in 60% of the SOS cases. Findings from each initiative were disseminated at national conferences and in peer-reviewed manuscripts beginning in 2003.

Conclusion—Retrospective review of clinical trials, case series, and FDA reports and prospective registries can provide important information on safety signals initially identified in licensing trials.

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Conflicts of interest

None.

Keywords

Adverse drug reactions; Acute myeloid leukemia; Hematopoietic stem-cell transplant; Veno-occlusive disease

1. Introduction

Adverse drug reactions (ADRs) are among the top ten leading causes of death. New approaches to identifying unexpected toxicities in the oncology setting are needed. We previously reviewed the established pharmacovigilance efforts of the Food and Drug Administration (FDA) and our independent State of South Carolina/National Cancer Institute-funded pharmacovigilance programs called the Southern Network on Adverse Reactions (SONAR) with respect to 50 drugs primarily used in the hematology and oncology settings [1]. We found that report quality for adverse drug reactions included in SONAR databases (primarily obtained directly from clinicians) was greater than for adverse events reported spontaneously to the FDA's Adverse Event Reporting System (FAERS) [1].

We report herein a case study comparing and contrasting findings and dissemination initiatives of SONAR and a pharmaceutical sponsored safety registry with respect to: case completeness; incidence estimates; and publication timeliness for one serious adverse drug reaction- sinusoidal obstructive syndrome (SOS) associated with gemtuzumab-ozoogamycin (GO). (The toxicity was initially termed hepatic veno-occlusive disease (VOD)) [4–8].

GO is the first antibody-drug immunoconjugate approved in the oncology setting. The anti-CD33 antibody is linked with calechimycin, which is then delivered to leukemia cells. GO received accelerated FDA approval in 2000 as monotherapy for older persons with relapsed AML at a dose of 9 mg/m^2 every 14 days, based on three phase II studies with 142 patients. Hepatic SOS, the focus of this study, occurred in 0.9% of patients in three phase II licensing trials.

Several serious ADRs among GO-treated patients in the post-marketing setting were reported to the FDA shortly after FDA approval was granted—prompting early postmarketing data review. A 2001 report from MD Anderson Cancer Center identified 14 GO-treated patients with acute myeloid leukemia who had developed hepatic veno-occlusive disease (VOD) following GO-administration in off-label clinical settings [2]. Safety concerns led the sponsor to revise the product label in 2001 indicating that risks of hepatic VOD were increased in patients who received GO either before or after hematopoietic stem-cell transplant (HSCT), patients with underlying hepatic disease or hepatic impairment, and patients who received GO with other chemotherapies. FDA also required the sponsor to initiate a registration program to ascertain adverse event risks following GO treatment in routine clinical settings. (The product was voluntarily withdrawn from the United States market in 2010 after a phase III clinical trial was terminated early when no improvement in clinical benefit was noted and after a greater number of deaths were identified in the group of patients who received GO compared to chemotherapy alone) [3].

2. Methods

2.1. Data sources

RADAR/SONAR databases consisted of FDA MedWatch reports and case series or clinical trials describing GO-associated SOS in peer-reviewed literature or personal communication from the Principal Investigator of a cooperative group clinical trial of pediatric acute myeloid leukemia (AML) [4,8]. The case definition included GO use for patients with AML or advanced myelodysplastic syndrome and clinical or laboratory findings consistent with the Seattle or Baltimore SOS criteria. In some instances, pathologic findings consistent with SOS were reported. A case report form included information on sociodemographics; clinical, laboratory, and pathology findings associated with the leukemia diagnosis and SOS; clinical trial participant; GO dose and schedule; outcome; and SOS date. Incidence was derived from phase I/II clinical trials, pilot studies, and observational studies reported from eight academic cancer centers. Relative risks were calculated for GO-associated SOS with or without SCT as well as with or without concomitant use of other chemotherapeutic agents.

A manufacturer sponsored registry of GO safety in routine clinical practice was requested by the FDA in 2001. Patients with AML who were to receive GO at approximately 60 study sites (90% were academic cancer centers) gave written consent for prospective abstraction of clinical and laboratory data of GO-treated individuals. Assessments were scheduled within one day of first GO infusions, weekly for six weeks after first GO doses, or 4 weeks after last GO doses, and six months after final GO doses. All serious adverse events and non-serious adverse events related to hepatotoxicity, hypersensitivity, infusion-related toxicity, pulmonary toxicity, and renal toxicity were monitored. SOS incidence was the primary outcome variable. All cases meeting the SOS clinical definition as judged by a study investigator and any potential SOS cases identified by review of hepatic adverse events by two hepatologists were included. Certainty of diagnosis was graded as possible, probable, or definite. Potential risk factors included demographics, social history, laboratory tests, GO doses, concomitant medications, liver history, and inflammatory disorders. Risk factors for SOS were assessed in two analyses—one comparing patients with SOS versus those without SOS and the second comparing patients with moderate/severe SOS versus others.

3. Results

3.1. Case information

Overall, 99 reports of SOS in GO-treated adult patients and six reports of SOS in GO-treated pediatric AML patients were identified in FDA's database by the academic pharmacovigilance initiative (Table 1) [4,8]. Hospitalization occurred in 80%; 66% died from SOS. Forty adult patients underwent autologous or allogeneic SCT prior to GO administration and six pediatric patients underwent allogeneic SCT after GO. Median time from GO administration to SOS occurrence for adult patients who did not undergo an allogeneic SCT was 10 days (range, 0–53 days) and 13 days following SCT procedures (range, 7–1 days) for AML patients who had previously received GO. Diagnostic findings included 5-fold elevations of hepatic aminotransferases, bilirubin >2 mg/dl, and painful hepatomegaly, ascites, or weight gain, occurring in >80% of SOS patients. Adult patients

received the FDA approved dose about two-thirds of the time and at the FDA approved schedule about 75% of the time. Over 40% of reports were from clinical trials, where GO was administered to younger AML patients or at schedules more frequently than day 1 and 15. Over 66% of GO-associated SOS patients died within 4 days of SOS occurrence.

For the sponsor's prospective registry of routine clinical practice, 482 GO-treated patients at 54 centers who received a mean dose of 7.8 mg/m^2 were included [5–7]. 135 potential SOS cases were evaluated by two hepatologists. Overall, 44 of these cases were classified as SOS- 31 as definite, 7 as probable, and 6 as possible SOS. Of these 44 SOS cases, 8 were mildly severe, 17 were moderately severe, and 19 were severe. Twelve SOS patients had undergone a prior HCT. Median time to peak bilirubin values was 2 weeks after the first GO dose. Over three fifths of patients who developed SOS had bilirubin values >34 μmol/L after first GO doses. The median time to peak transaminase evaluation was 7–12 days after first GO doses. Overall, 13 patients died from SOS within 6 months of follow-up. Overall, 41% of the 482 patients had received concomitant chemotherapy, 18% had undergone prior SCT, and 60% of SOS patients died from SOS.

3.2. Incidence estimates and risk factors

For the academic pharmacovigilance initiative, among adult AML patients treated in clinical trials, SOS occurred at a rate of 3% with GO monotherapy at FDA approved dosing and scheduling (9 mg/m^2 on days 1 and 15); 7% when the drug was used with other hepatotoxic chemotherapeutic agents, and 28% when GO and 6-thioguanine were co-administered. Among 129 pediatric AML patients who did not undergo SCTs and who received GO at doses less than the FDA approved doses or in conjunction with daunorubicin, cytarbine, or etoposide, SOS incidence was 4%. Among 162 GO-treated patients in clinical trials, incidence rates were 38% and 16% when AML patients underwent allogeneic or autologous SCT before GO administration, respectively; and 37% when GO was administered prior to allogeneic SCT. Among 15 pediatric patients in clinical trials who received GO monotherapy and subsequent SCT, 40% developed SOS. Data was obtained for patients who received GO at 60 sites.

From the prospective sponsor registry, 54 clinicians at 54 cancer centers reported on 482 evaluable patients [5,6]. Overall, the SOS incidence rate was 9.1%. No risk factors for SOS development were identified in multivariate analyses that included information on smoking history, alcohol use, baseline hepatic function, and prior hepatic disease.

3.3. Comparison of findings

The RADAR/SONAR effort and the Registry effort were com-pared. RADAR/SONAR included twice as many SOS reports as the sponsor's registry (99 versus 44). Data elements related to hepatic function test results, GO dosing and scheduling, concomitant chemotherapy use, SOS onset, and outcome were included in both databases, although completeness was virtually 100% in the manufacturer's registry. The manufacturer's registry included prospectively collected data facilitating determination of certainty of SOS diagnosis and SOS severity, while this was not possible with the RADAR/SONAR data. Multivariate analyses seeking to identify risk factors were evaluated only in the sponsor's

registry, because of absence of complete data on concomitant drugs, smoking history, and baseline hepatic function in the RADAR/SONAR Registry. Findings from each study were published in the peer-reviewed literature and presented at national medical conferences, beginning in 2003 [4–8].

4. Comment

In this review of GO-associated SOS pharmacovigilance initiatives, information obtained by an academic pharmacovigilance investigation and a sponsor supported registry independently identified GO-associated SOS as an important and serious safety concern. While the methods of obtaining these data differed (primarily retrospective versus prospective data collection efforts), the findings and dissemination efforts were similar. In interpreting our findings, several factors should be considered.

Pharmacovigilance by leukemia specialists prompted early FDA review of post-marketing safety data. Reports from the first six months of marketing identified three serious adverse events—hypersensitivity reactions, pulmonary toxicity, and hepatotoxicity. On the basis of these reports, in 2001, the FDA's Division of Oncology Drug Products requested Black Box warnings from the sponsor and required initiation of a registration program to determine SOS incidence, risk factors, and adverse events in routine care settings. The academic investigation was initiated when a clinician from MD Anderson contacted the Principal Investigator of RADAR/SONAR about 14 cases of GO-associated SOS that had occurred at his cancer center.

The findings can be compared to safety assessments from regulatory agencies in Japan, Europe, and the United States [3,9,10]. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) conducted a safety review in 2011. The drug had received PMDA approval in 2005 for the same indication as in the FDA and post-approval, 3000 persons in Japan received GO. A use-survey evaluated 852 patients in Japan between 2005 and 2009, of whom 753 were included in safety evaluations. A 5.6% SOS incidence rate was noted. PMDA concluded that no change in the risk-benefit profile for GO as monotherapy for older patients with AML had been identified. The European Medicines Agency (EMA) assessed GO in 2008. Overall, 16 episodes of VOD (in 15 patients) were identified (5% incidence). VOD incidence in GO-treated patients who had no prior or subsequent HSCT was 1%; 19% for patients with HSCT history prior to GO administration; and 16% for patients receiving HSCT after GO administration. The safety assessment was included in a EMA assessment report for GO where the EMA did not approve the product for marketing [10]. In 2001 in the United States, the manufacturer added Black warnings to the package insert warning that patients who receive GO either before or after HSCT, patients with underlying hepatic disease or abnormal liver function, and patients receiving GO in combinations with other chemotherapy are at increased risk for developing VOD, including severe VOD. FDA reported in 2006 that preliminary results from the Registry identified a 10% GO-associated VOD occurrence rate and higher rates among patients who received HSCT before or after receiving GO.

RADAR/SONAR findings and the sponsor's registry findings were disseminated at national conferences and in peer-reviewed manuscripts [4–8]. Safety information remains important as a recent phase III clinical trial identified that first line therapy with low-dose GO as compared to best supportive care, significantly improved overall survival in older patients with AML, no unexpected adverse events were identified, and toxicity was manageable [11]. Hence, there is support for re-introducing GO in the United States and approving GO for the first time in Europe.

We conclude that findings from the two independent pharmacovigilance efforts extend safety concerns initially reported in 2001 [2]. Retrospective reviews of an academic safety review of FDA data supplemented by clinical trial and observational case series reports and a prospective safety registry independently identified similar findings for GO-associated SOS and disseminated these findings at presentations and in manuscripts.

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Table 1

Descriptive data of acute myeloid leukemia patients prescribed Gemtuzumab Ozogamycin (GO) in an academic pharmacovigilance initiative and a sponsor supported prospective registry of routine clinical practice.

	Academic registry	Sponsor supported registry
Number of individual cases	99	44
Age (years) mean	– **	61.5
Participating medical centers	60	54
Overall incidence (%)	Not reported	9.1
Incidence with concomitant drug use (%)	7	Not reported
Deaths among SOS patients (%)[a]	66	30
Hospitalized (%)	80	Not reported
Autologous SCT SOS incidence (%)	16	Not reported
Allogeneic SCT SOS incidence (%)	38	Not reported
Median time from GO administration to SOS occurrence (allogeneic)	10 days	Not reported
Median time from GO administration to SOS occurrence (post-SCT)	13 days	Not reported
Median time to peak bilirubin	– **	2 weeks
Risk factors (multivariate analyses)	Not conducted	None identified
Data/literature published	2003, 2007	2003, 2007, 2013
Voluntary removal of drug from market	2010	

SCT = Stem cell transplant.

[a]Exact two-tailed $p < 0.034$.