The Safety of Antibody Drug Conjugates: A Literature Review

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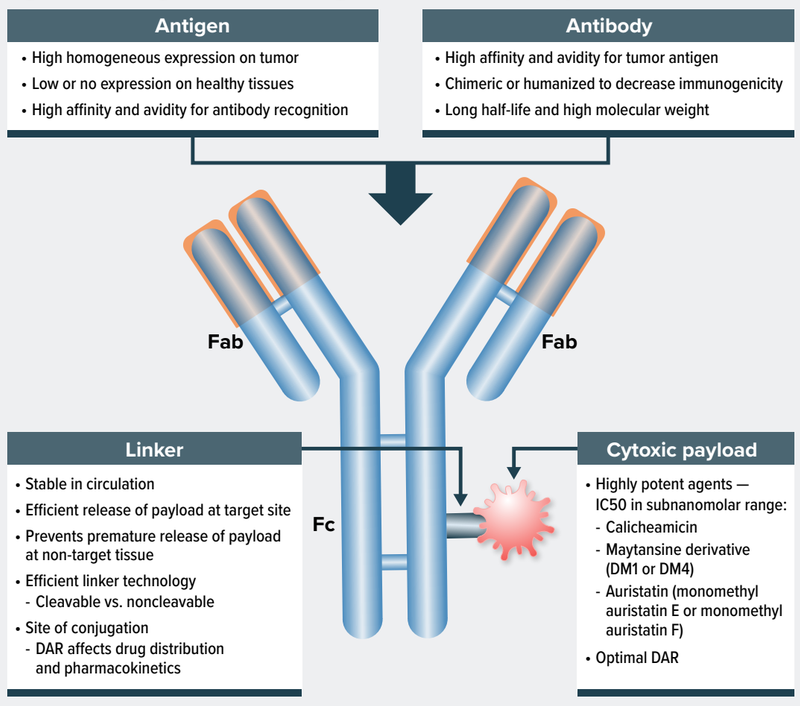
DISCLOSURES

Joan Forns, James Kaye, and Andrea Margulis are full-time employees of RTI Health Solutions, a unit of RTI International, which is a nonprofit organization that conducts work for government, public, and private organizations, including pharmaceutical companies. Fabio A. Lievano and Jerzy E. Tyczynski are employees of AbbVie Inc.

BACKGROUND

- Antibody-drug conjugates (ADCs) are a class of targeted therapies for cancer that combine the relative selectivity of a monoclonal antibody with a cytotoxic agent joined covalently by a cleavable or noncleavable chemical linker (Figure 1).
- A large number of ADCs are under evaluation in clinical trials worldwide, but only 5 had been approved by both the United States Food and Drug Administration and the European Medicines Agency at the time of this literature review (July 2019): brentuximab vedotin (BV), ado-trastuzumab emtansine (T-DM1), gemtuzumab ozogamicin (GO), inotuzumab ozogamicin (IO), and polatuzumab vedotin (PV).

Figure 1. Diagram Describing the Different Components of an ADC



DAR = drug-antibody ratio; Fab = antigen-binding fragment; Fc = constant fragment; IC50 = half maximal inhibitory concentration.

OBJECTIVE

- To identify the most common adverse events (AEs) reported from phase 2-4 clinical trials or observational studies for the 5 study ADCs.

METHODS

- A targeted review of literature published from 2015 through July 2019 was conducted in PubMed and Embase to identify peer-reviewed, English-language articles reporting AEs associated with the use of ADCs with at least 20 patients in each arm.
- Level 1 (titles and abstracts) and level 2 (full-text review) screening were conducted by 1 epidemiologist, and final decisions regarding inclusion of publications were made based on consensus with a senior epidemiologist when necessary.
- We first extracted AEs of any grade reported in at least 10% of patients in each study. In a second step, we summarized the reported incidence for each AE and ADC by calculating the median incidence proportion across all studies reporting a particular AE with at least 10% incidence. The median was calculated to reduce the effect of extreme values (outliers) for any particular AE.
- We also calculated the median reported incidence of AEs of any grade stratified by combinations of payload (cytotoxic agent) and linker.

RESULTS

- The literature search identified 357 unique publications. After reviewing titles and abstracts, we selected 58 articles for full-text review: 48 of these qualified for data extraction. Among the 48 selected studies, 18 (38%) reported AEs for BV, 15 (31%) for T-DM1, 7 (15%) for GO, 7 (15%) for IO, and 1 for PV (2%) (Figure 2).
- Most included articles reported on both efficacy and safety; 40 reported on clinical trials (22 phase 2, 17 phase 3, and 1 phase 4), and 8 reported on observational studies.
- For the 2 ADCs with the largest numbers of included studies, BV and T-DM1, the median incidences of AEs of any grade were higher for BV than for T-DM1 for anemia (31% vs. 24%), neutropenia (32% vs. 13%), thrombocytopenia (57% vs. 29%), peripheral sensory neuropathy (23% vs. 13%), fatigue (40% vs. 30%), nausea (40% vs. 36%), vomiting (26% vs. 18%), and diarrhea (29% vs. 18%) (Figure 2). However, median incidences were lower for BV than for T-DM1 for anorexia (18% vs. 21%), pyrexia (19% vs. 25%), myalgia (12% vs. 16%), and headache (14% vs. 27%).
- IO was associated with higher median AE incidences than BV and T-DM1 for neutropenia (42%), thrombocytopenia (72%), fatigue (45%), nausea (49%), and pyrexia (32%).
- For GO, safety information was scarce; the median incidence was 45% for thrombocytopenia, 45% for increased aspartate aminotransferase (AST), and 50% for fatigue. Finally, PV had the highest incidence of fatigue (60%) and diarrhea (47%) based on a single study.
- GO and IO have a calicheamicin derivative payload and an acid-labile (cleavable) hydrazine-based linker. For most of the AEs, these ADCs showed higher median AE incidence than other types of payload/linker combinations.
- BV and PV have a monomethyl auristatin E (payload) and a protease-cleavable linker. T-DM1 has DM1 (derivative of maytansine) as payload and a noncleavable thioether linker. For these 3 ADCs, the median incidences of most AEs of any grade were similar, including anemia, thrombocytopenia, constipation, nausea, vomiting, diarrhea, anorexia, pyrexia, myalgia, and cough. ADCs with monomethyl auristatin E (payload) as the payload and a protease-cleavable linker had a higher incidence of neutropenia, peripheral sensory neuropathy, and fatigue relative to the ADC with a DM1 payload and noncleavable thioether linker.

Figure 2. Flowchart of Included Articles

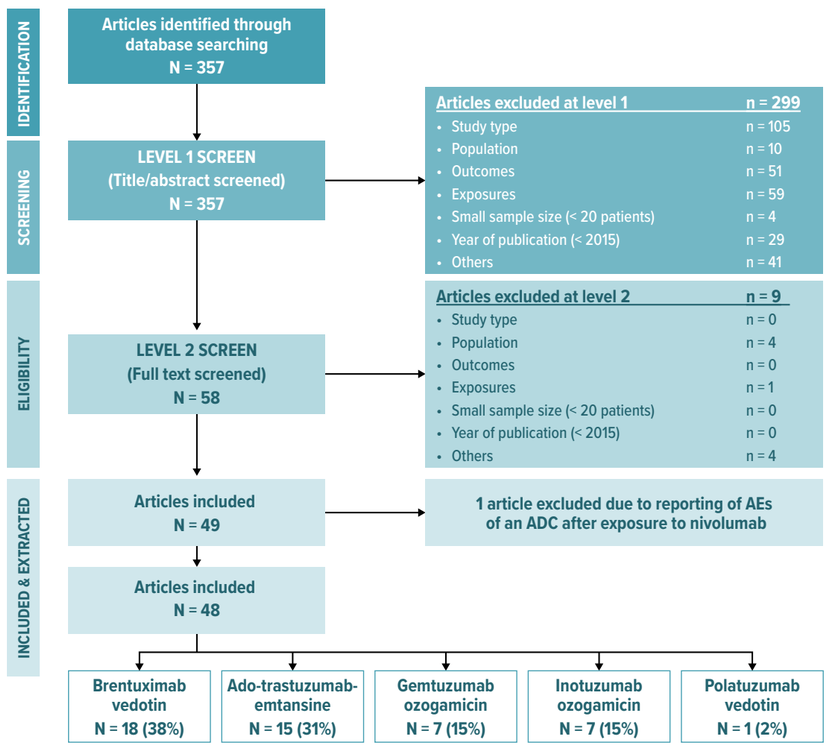
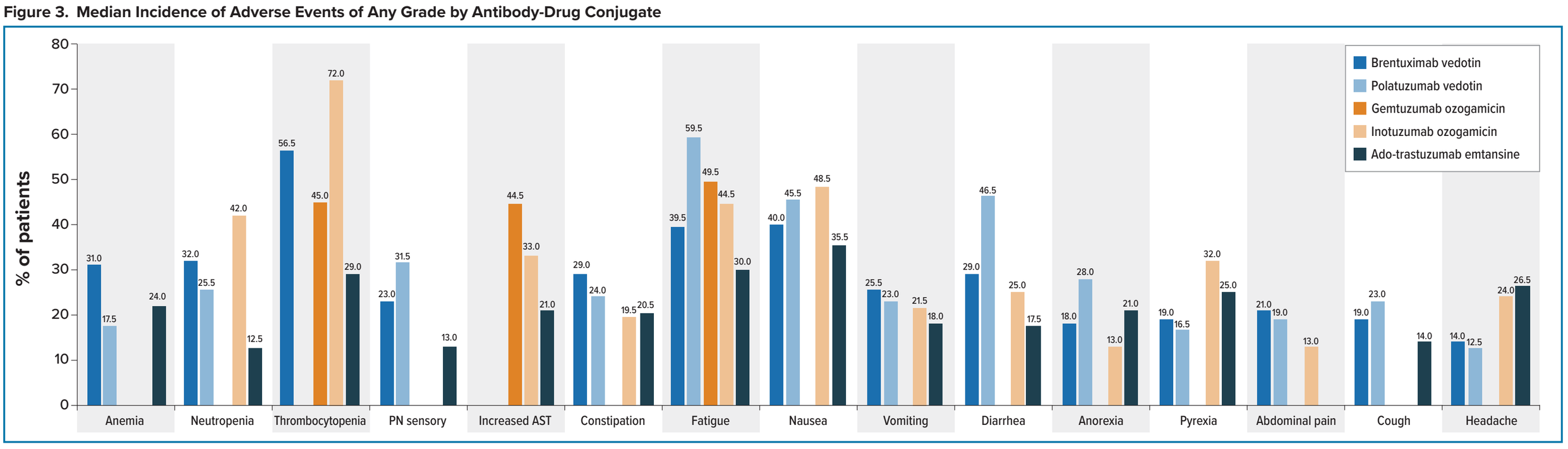
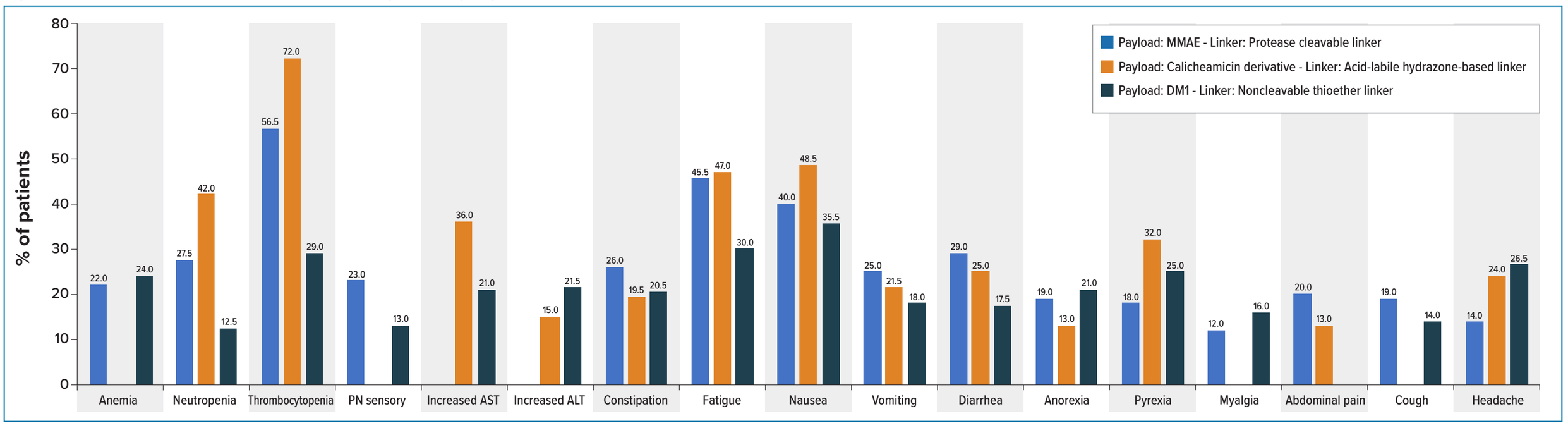


Figure 3. Median Incidence of Adverse Events of Any Grade by Antibody-Drug Conjugate



ALT = alanine aminotransferase; DM1 = derivative of maytansine; MMAE = monomethyl auristatin E (payload); PN = peripheral neuropathy.

Figure 4. Median Incidence of Adverse Events of Any Grade by Payload and Linker



DISCUSSION

- For BV, the AEs reported in the largest number of studies were peripheral sensory neuropathy, diarrhea, and neutropenia. The AEs of any grade with the highest median incidence were peripheral sensory neuropathy, nausea, and fatigue.
- For T-DM1, the AEs reported in the largest number of studies were epistaxis, thrombocytopenia, nausea, and headache. Anemia, fatigue, and thrombocytopenia had the highest median incidence among all AEs of any grade.
- For IO, increased AST and thrombocytopenia were the most commonly reported AEs of any grade. Of the 5 ADCs in this review, IO had the highest incidence of neutropenia and thrombocytopenia.
- For GO, information on safety was scarce. Febrile neutropenia was the most commonly reported AE of any grade. GO showed the highest median incidences among all ADCs for increased ALT or AST and for anorexia/decreased appetite.
- Only 1 article reported safety data for patients treated with PV. The AE of any grade with the highest incidence was fatigue.
- **Strengths:** The present review comprehensively considered AEs of approved ADCs for both clinical trials and observational studies; AEs were stratified by payload/linker combination.
- **Limitations:** The extraction of AEs with an incidence of at least 10% likely overestimated the true median incidence of a particular AE across all studies (because any studies with lower than 10% incidence for a particular AE are omitted from the calculation). AEs were likely ascertained and reported differently in clinical trials versus observational studies. AEs of any grade are reported collectively here. Clinical trials are not powered for safety. Therefore, some important AEs that occur less commonly may become apparent only after the product is approved when larger-size studies can be performed.

CONCLUSIONS

- The 5 approved ADCs were found to have somewhat distinct safety profiles. Most studies, especially most observational studies, reported on BV and T-DM1, which have been in the market longer than the other ADCs.

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