Toxicity Management

Development of a novel and immune-mediated adverse events algorithm

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BACKGROUND: Novel immunotherapy and biologic agents are being developed with the potential to improve outcomes and reduce long-term toxicities among individuals with hematologic malignancies. These emerging drugs affect neoplastic cells and the surrounding microenvironment, causing unique immune-mediated toxicities.

OBJECTIVES: The aim was to develop an algorithm for clinical staff to manage unique toxicities associated with next-generation immunotherapies indicated in the hematologic population, using a system-focused approach.

METHODS: Data were collected using specific toxicities based on the four major novel biologic classes. Immune-mediated adverse events were reported across studies. Based on published literature, institutional experience, and group consensus, a novel algorithm for managing immune-mediated toxicities was created.

FINDINGS: The development of this treatment algorithm provides a more streamlined approach for managing common but unique toxicities and improves safety, compliance, patient outcome, and quality of life with novel immuno-oncologic agents.

KEYWORDS immunotherapy; toxicities; novel agents; immune-mediated; adverse events

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TWO MAJOR LYMPHOMA CATEGORIES EXIST, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). These two categories comprise a group of lymphoproliferative diseases with an incidence of 55,000–60,000 new cases each year (Alinari, Quinion, & Blum, 2015). The foundation of treatment for B-cell lymphomas consists of traditional chemotherapy agents, including alkylating agents, anthracyclines, purine analogs, and monoclonal antibodies. To date, the mainstays of treating NHL are dependent on the specific subtype of lymphoma. Indolent lymphomas, such as follicular lymphoma (FL), marginal zone lymphoma (MZL), and small lymphocytic lymphoma (SLL), may be managed using an observation-only approach (Horning & Rosenberg, 1984; Yuda et al., 2016), a single-agent monoclonal antibody (Weiner, 2010), or a combined chemotherapeutic approach (Rummel et al., 2013). In comparison, more aggressive lymphomas are almost always treated with traditional chemotherapy regimens, such as rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Adriamycin®), vincristine (Oncovin®), and prednisone (Deltasone®), also known as R-CHOP (Feugier et al., 2005; Peyrade et al., 2017). HL is generally treated with doxorubicin, bleomycin (Blenoxane®), vinblastine (Alkaban®), and dexamethasone (Decadron®), also known as ABVD (Diefenbach et al., 2016; Meyer et al., 2005). Traditional chemotherapeutic approaches are associated with nonspecific toxicity, including myelosuppression, mucositis, alopecia, fatigue, nausea, and vomiting, which are related to the drug’s cytotoxic effect on normal cells (Bhatt, Alejandro, Michael, & Ganetsky, 2014).

Novel biologic agents are being developed with the potential to improve outcomes and reduce long-term toxicities. New cellular targets have been identified, leading to the development and introduction of specific nonchemotherapeutic regimens. These targets include regulators of the cell cycle and specific surface antigens (Alinari et al., 2015). Targeted therapy has the potential to increase efficacy related to its highly specific nature. In addition, this direct activity allows for fewer cytotoxic effects on normal cells compared with traditional chemotherapy agents (Bhatt et al., 2014).

Four major novel biologic classes are in development or have recently received U.S. Food and Drug Administration (FDA) approval for patients with hematologic malignancies, and specifically those with B-cell lymphomas: immunomodulatory drugs (IMiDs), programmed death-ligand 1...
(PD-1) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, and Bruton’s tyrosine kinase (BTK) inhibitors. These emerging agents affect neoplastic cells and the surrounding immune microenvironment, namely the context in which immune effector cells illicit a pro-inflammatory response causing unique immune-mediated toxicities, including dermatologic, gastrointestinal, hepatic, endocrine, pulmonary, and other less common inflammatory events (Bhatt et al., 2014; Coutuë et al., 2015; Nastoupil & Neelapu, 2015; Ruan, Shah, Martin, & Schuster, 2016). Although the exact mechanism of many of these unique toxicities is unknown, they may, in part, occur secondary to the activation of immune effector cells (e.g., T cells, natural killer cells, macrophages), causing a systemic proinflammatory response. These cells may also target normal tissue and, therefore, create an autoimmune-like reaction, commonly termed immune-mediated toxicities. Mild cytopenias are also seen with these new immune-mediated agents (Ansell et al., 2015; Batlevi, Matsuki, Brentjens, & Younes, 2016; Bröckelmann, Borchmann, & Engert, 2016; Matsuki & Younes, 2016; Wang et al., 2013). Effective management of these toxicities requires understanding of the incidence and severity of common adverse events associated with these new agents. To date, no known evidence-based algorithm has been published related to the management of immune-mediated toxicities in patients with lymphoma undergoing immunotherapy treatment.

The objective of this evidence-based practice initiative was to develop treatment algorithms to effectively guide care of patients experiencing emerging toxicities with novel immuno-oncologic agents. The development of effective algorithms to ameliorate serious toxicities can contribute to improved patient safety and quality of life and standardize practice among providers.

### Methods
A literature review was conducted using PubMed, EMBASE®, the Cumulative Index to Nursing and Allied Health Literature (CINAHL®), Scopus, and the Cochrane Library databases. The search criteria included the following keywords and medical subject heading (MeSH) terms: non-Hodgkin lymphoma, Hodgkin lymphoma, adverse effects, drug-related side effects, adverse reactions, toxicity, and immunotherapy, as well as drug classes (PD-1, BTK inhibitors, IMiDs, PD-1) and specific drug names (Ibrutinib and Imbruvica). A total of 21 publications were identified that met the search criteria. After identifying published data fitting the search criteria, data on toxicity were gathered, including grade (grade 1–2 or grade 3–4), intervention, and outcomes, and categorized based on the four major novel biologic classes: IMiDs, PD-1 inhibitors, BTK inhibitors, and PI3K inhibitors.

### Literature Review
Data were collected using the studies in which common immune-mediated toxicities were identified. Common toxicities were separated by severity (grade 1–2 or grade 3–4). Analysis focused on the following major body systems and organs affected by toxicity:

“Many next-generation therapies are associated with unique and sometimes serious adverse events.”

### Table 1.

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>AGENT</th>
<th>GRADE 1–2 TOXICITY</th>
<th>GRADE 3–4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK inhibitor</td>
<td>Ibrutinib (Imbruvica®), Acalabrutinib, ONO-4059</td>
<td>Diarrhea, 65% or less; rash, 50% or less; thrombocytopenia, 8%; neutropenia, 2%</td>
<td>Neutropenia, 70% or less; thrombocytopenia, 45% or less; pneumonia, 25% or less; anemia, 10% or less; diarrhea, 6% or less; rash, 2%</td>
</tr>
<tr>
<td>IMiD</td>
<td>Thalidomide (Thalomid®), Lenalidomide (Revlimid®), Pomalidomide (Pomalyst®)</td>
<td>Rash, 35% or less</td>
<td>Neutropenia, 83% or less; thrombocytopenia, 47% or less; pneumonia, 25% or less; anemia, 20% or less; rash, 7% or less; pneumonia, 3%</td>
</tr>
<tr>
<td>PD-1 inhibitor</td>
<td>Pembrolizumab (Keytruda®), Nivolumab (Opdivo®)</td>
<td>Rash, 35% or less; diarrhea, 28% or less; thrombocytopenia, 17%; pneumonia, 11% or less</td>
<td>Pneumonitis, 22% or less; thrombocytopenia, 22%; colitis, 5%</td>
</tr>
<tr>
<td>PI3K inhibitor</td>
<td>Idevalisib (Zydelig®), Duvelisib, TGR-1202</td>
<td>Diarrhea, 47% or less; transaminitis, 31%; pneumonia, 17% or less</td>
<td>Diarrhea, 14% or less; transaminitis, 6%; pneumonia, 5% or less</td>
</tr>
</tbody>
</table>

BTK—Bruton’s tyrosine kinase; IMiD—immunomodulatory drug; PD-1—programmed death ligand 1; PI3K—phosphoinositide 3-kinase

**Note.** Included studies used varying versions of the Common Terminology Criteria for Adverse Events. Refer to studies for more specific information.

**Note.** Based on information from Alinari et al., 2015; Ansell et al., 2015; Batlevi et al., 2016; Bhatt et al., 2014; Bumel & Broadway-Duran, 2014; Bröckelmann et al., 2016; Cheah & Fowler, 2016; Coutuë et al., 2015; de Claro et al., 2015; Desai et al., 2015; Flinn et al., 2014; Fowler et al., 2015; Gonzalez-Rodriguez et al., 2015; Leonard et al., 2015; Matsuki & Younes, 2016; Ruan et al., 2016; Smith, 2015; Tinsley et al., 2015; Tusciano et al., 2014; Villadolid & Amin, 2015; Wang et al., 2013.
integumentary (rash), gastrointestinal (diarrhea/colitis), respiratory (upper respiratory infections [URIs] and pneumonitis), hematologic (cytopenias), and hepatic (transaminitis). The common immune-mediated toxicities identified in the 21 reviewed articles are presented in Table 1.

Development of the Algorithm
The findings of the literature review were reviewed with an interprofessional group consisting of physicians, advanced practice providers (APPs), and RNs at a 672-bed National Cancer Institute–designated comprehensive cancer center, serving about 1,700 patients with lymphoma and 500 patients with myeloma annually. This evidence, along with the clinical experience of the providers, was used to develop a management algorithm for the most common immune-mediated toxicities observed in patients with lymphoma. The Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, was used as the framework for this algorithm (Trotti et al., 2003).

CTCAE was originally created for standardization of grading adverse events in oncology research. As new oncologic treatment modalities have emerged, new and unique toxicities have been identified. The CTCAE criteria provides a streamlined guide to report AEs in research publications. These reports have aided in the overall safety and monitoring of adverse event reporting. Currently, the use of the CTCAE criteria is the mainstay of grading adverse events related to oncologic agents. Clinical staff must be educated to recognize and grade these toxicities. With the use of the CTCAE criteria, implementing the grading scale and, therefore, implementing a treatment management strategy for the reported toxicity is much easier. Educating staff and clinicians in the community about new and unique toxicities can improve patient safety outcomes as novel agents continue to be introduced as the new mainstay for lymphoma therapies.

Findings
The resulting algorithm has been implemented into practice to inform the management of patients with immune-mediated toxicities. The use of the algorithm is highlighted in two patient cases.

Case Study 1
A 61-year-old woman with relapsed stage IV, grade 2 FL received an oral PI3K inhibitor. She had no history of irritable bowel syndrome, malabsorption, or malignancy in the gastrointestinal tract. The patient developed diarrhea after cycle 5, consistent with previous reports in published literature of PI3K inhibitors causing diarrhea and colitis (Coutré et al., 2015). She presented to clinic in stable condition but reported diarrhea eight times per day. The patient’s stools were watery and unformed. She noted no changes to her diet, no increased stressors to her life, had no recent travel, and was not recently on antibiotics. The patient’s diarrhea was evaluated as grade 3 using the CTCAE guidelines, and the patient’s medication was held per the algorithm guidelines. The patient’s diarrhea worsened with concerns for colitis (grade 4 diarrhea). Per the algorithm, the patient had a colonoscopy, which was negative for colitis. The patient was initiated on a budesonide (Entocort®) taper, as recommended in Coutré et al. (2015). After three weeks, the patient’s diarrhea continued to improve, and the patient was able to be rechallenged with the PI3K inhibitor. On re-exposure, diarrhea was not observed.

Case Study 2
In the second case, a 74-year-old woman with relapsed lymphoma received a PD-1 inhibitor. She had no history of lung disease, chronic obstructive pulmonary disease, or compromised cardiac function. During cycle 3, the patient reported progressive dyspnea and a nonproductive cough. The patient was evaluated clinically. The observed pulmonary toxicity was consistent with published literature on various PD-1 inhibitors (Jezeršek Novaković, 2015; Nastoupil & Neelapu, 2015). Oxygen saturation at rest was 100%, but decreased to 90% when the patient ambulated in the clinic hallway. Treatment was immediately held for suspicion of pneumonitis, and a workup with a chest x-ray and chest computed tomography (CT) was obtained. CT demonstrated new focal ground glass opacities and interstitial thickening along the minor fissure in the right upper and middle lobes, suggestive of inflammation. The patient was immediately started on high-dose corticosteroids for suspected pneumonitis. The patient had no improvement in the first week, so corticosteroid treatment was continued. After two weeks of high-dose steroids, the patient’s dyspnea improved and her nonproductive cough improved. A steroid taper over three weeks was recommended. When the patient was rechallenged with a PD-1 inhibitor, pneumonitis recurred. The patient was reinitiated on high-dose corticosteroids and the PD-1 inhibitor was permanently discontinued as per the algorithm.

Discussion
The algorithm (see Figures 1 and 2) was created to help streamline the management of common immune toxicities not seen with traditional chemotherapeutic agents. Treating lymphoproliferative diseases with immune-mediated agents often causes toxicities with an inflammatory response. Rash, transaminitis, inflammation of the gastrointestinal tract leading to diarrhea and colitis, respiratory infections, and pneumonitis were most commonly identified in the literature. Patients may experience mild

IMPLICATIONS FOR PRACTICE
- Educate staff and clinicians about novel agents being introduced for lymphoma therapies.
- Recognize that treating lymphoproliferative diseases with immune-mediated agents often causes toxicities with an inflammatory response.
- Use a clinical management algorithm to manage adverse events reported with the use of novel therapies.
to moderate cytopenias but, in a majority of cases, patients do not experience grade 3–4 events.

It also has been noted that new toxicities can arise when novel biologic agents are combined. A clinical trial combination of lenalidomide (Revlimid®), idelalisib (Zydelig®), and rituximab produced unacceptable toxicities and led to two patient deaths (Cheah et al., 2015). The combination of these immune-mediated agents led to fatal hepatotoxicity in one patient and colitis leading to fatal septic bacteremia in another. Of the seven patients in the study, six developed some degree of

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**FIGURE 1.**
GRADE 1–2 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENT IMMUNE-MEDIATED TOXICITIES

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Skin</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: Diarrhea and colitis</td>
<td>Covers less than 30% of body surface area</td>
<td>Monitor every 2–3 days; hospitalize</td>
</tr>
<tr>
<td>Continue therapy</td>
<td>Symptomatic therapy</td>
<td>Infectious disease and pulmonary consults</td>
</tr>
<tr>
<td>Delay therapy</td>
<td>Continue therapy</td>
<td></td>
</tr>
<tr>
<td>Symptomatic treatment</td>
<td></td>
<td>If symptoms persist, treat as grade 3–4.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th></th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Thrombocytopenia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Delay therapy: Check counts every 4–5 days.</td>
<td>Delay therapy: Check counts every 4–5 days.</td>
<td>Delay therapy: Check counts every 4–5 days.</td>
</tr>
<tr>
<td>Consider transfusion if hemoglobin is less than 8 g/dl.</td>
<td>Consider transfusion if platelet is less than 15 k/µl.</td>
<td>Consider growth factor support.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue LFT monitoring.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue therapy.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 1: AST or ALT greater than ULN – 3 x ULN; bilirubin greater than 1.5 x ULN</th>
<th>Grade 2: AST or ALT greater than 3–5 x ULN; bilirubin greater than 1.5–3 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue therapy</td>
<td>Delay therapy: Monitor AST/ALT every three days.</td>
</tr>
<tr>
<td></td>
<td>If AST/ALT continues for 5–7 days or worsens, 0.5–1 mg/kg per day methylprednisolone is indicated.</td>
</tr>
<tr>
<td></td>
<td>Treat as grade 2 or grade 3–4.</td>
</tr>
</tbody>
</table>

ALT—alanine aminotransferase; AST—aspartate aminotransferase; LFT—liver function test; ULN—upper limit of normal

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FIGURE 2.
GRADE 3–4 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENT IMMUNE-MEDIATED TOXICITIES

**Gastrointestinal**
- **Diarrhea**
  - Discontinue or delay therapy.
  - Consider 1–2 mg/kg per day methylprednisolone.
  - Consider prophylactic antibiotics for opportunistic infections.
  - Consider colonoscopy.
- **Colitis**
  - Discontinue or delay therapy.
  - Consider 1–2 mg/kg per day methylprednisolone.
  - Consider prophylactic antibiotics for opportunistic infections.

**Hematologic**
- **Anemia**
  - Discontinue or delay therapy.
  - Consider transfusion if hemoglobin is less than 8 g/dl.
  - 1–2 mg/kg per day methylprednisolone

**Skin**
- Covers more than 30% of body surface area or life-threatening
- Discontinue or delay therapy.
- Skin biopsy
- 1–2 mg/kg per day methylprednisolone

**Respiratory**
- Severe symptoms, hypoxia, or life-threatening
- Discontinue or delay therapy.
- Dermatology consult
- 2–4 mg/kg per day methylprednisolone
- Consider prophylactic antibiotics for opportunistic infections.
- Consider bronchoscopy.

**Hepatic**
- AST or ALT greater than 5 x ULN; bilirubin greater than 3 x ULN
- Discontinue therapy.
- Monitor AST/ALT every 1–2 days.
- 1–2 mg/kg per day methylprednisolone
- Consult gastroenterologist.
- If no improvement in 3–5 days, or AST/ALT worsens or rebounds, add 1 g twice daily mycophenolate mofetil.

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transaminitis (grade 2, 3, or 4 hepatotoxicity). Ultimately, the study was closed and the conclusion was made that the triplet was unsafe. It was, however, noted that doublet therapy of rituximab plus lenalidomide or rituximab plus idelislib was not associated with severe hepatotoxicity (Cheah et al., 2015). The current study suggests the importance of evaluating not only the toxicities of several individual agents, as outlined in the algorithm, but also the cumulative toxicities of combined therapies as they continue to emerge.

Implications for Practice

The two presented cases serve as examples of the unique toxicities seen with today’s newer agents to treat lymphomas. Clinical and research nurses, as well as APPs, are well positioned to identify novel toxicities as they occur related to their critical role in side effect education and management. Therefore, educating and informing clinicians on how to identify, grade, and manage these potential unique toxicities associated with immune-mediated therapies is important. In this project, the interprofessional team members were educated on how to effectively grade each toxicity and follow the algorithm to improve patient outcomes and health and decrease morbidity and mortality in patients. Early intervention, including supportive care, medications, and/or holding or discontinuing the drug, is essential to minimize the likelihood of permanent or severe side effects. Although the toxicities may be similar to those experienced by patients undergoing chemotherapy or radiotherapy, the mechanisms causing them are distinct, and, therefore, such toxicities are managed differently than traditional chemotherapy toxicities.

As these drug classes continue to be explored and developed, potential exists for similar toxicities and adverse events to be reported across other malignancies and disease sites. Clinical management algorithms should continue to be implemented into the management of these novel therapies as reported adverse events become more common.

Conclusion

Nonchemotherapeutic approaches hold enormous promise for patients with lymphoma. Many of these next-generation therapies are associated with unique and sometimes serious adverse events. The development of the treatment algorithm provides a more streamlined approach to manage these unique toxicities. It also creates a standardized method to evaluate, monitor, and manage events as they occur. Ultimately, institution of standardized guidelines for clinical staff coupled with timely management of adverse events will lead to improved outcomes and improved quality of life.

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