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Advances in Hodgkin Lymphoma Treatment: Clinical Considerations for Managing Toxicities in Nivolumab-AVD Therapy

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Abstract

The treatment landscape for advanced-stage Hodgkin lymphoma (HL) continues to evolve, with immune checkpoint inhibitors now pivotal to improving patient outcomes. One of the most promising developments is the nivolumab-AVD regimen, which combines nivolumab with doxorubicin, vinblastine, and dacarbazine. This novel approach has demonstrated encouraging efficacy and is increasingly integrated into frontline treatment regimens. This article provides practical, evidence-based knowledge for advanced practitioners to effectively manage the most common toxicities associated with nivolumab-AVD. It reviews the most frequently observed adverse events, including immune-mediated events, and outlines best practices for monitoring and management. A real-world case study illustrates how proactive management and clinical judgment can influence outcomes in patients receiving nivolumab-AVD.

CASE STUDY

A 23-year-old male presented with a 1-month history of unintentional weight loss and recurrent night sweats occurring one to two times per week. His medical history included sickle cell trait but was otherwise unremarkable. Due to anemia and a family history of chronic lymphocytic leukemia in a grandparent, he was referred to a leukemia specialist for further evaluation and concern for a possible malignancy. During the workup, a PET-CT scan revealed lymphadenopathy both above and below the diaphragm. The spleen was normal in size but demonstrated several foci of moderately increased hypermetabolic activity. A core biopsy of a right supraclavicular lymph node confirmed a diagnosis of classical Hodgkin lymphoma. Staging studies classified the disease as stage IIIB (advanced stage).

Classical Hodgkin lymphoma (cHL) is a rare subtype of lymphoma characterized by the presence of Reed–Sternberg cells, which are large, abnormal cells typically found in lymph node tissue. It is considered a highly curable malignancy. However, advanced-stage disease presents more complex treatment challenges, often requiring intensive immunosuppressive regimens and long-term management.

Traditional first-line therapies combine chemotherapy with radiation, achieving high cure rates. However, relapse, long-term toxicity, and diminished quality of life remain significant concerns. In recent years, the introduction of immune checkpoint inhibitors, particularly those targeting the programmed cell death protein 1 (PD-1) pathway, has offered a novel and effective therapeutic option (Brice et al., 2021).

NIVOLUMAB-AVD

Nivolumab (nivo; Opdivo) is a PD-1 inhibitor that blocks the PD-1/programmed cell death ligand 1 (PD-L1) interaction, which is known to inhibit the normal activity of cells in the microenvironment of cHL tumors. The safety profile of this drug was evaluated in 266 adult patients with cHL in the CheckMate 205 trial and in 23 patients in the CheckMate 039 trial. The most frequently reported severe adverse events included infections, most commonly upper respiratory tract infections (44%), followed by fatigue (39%), productive cough (36%), and gastrointestinal disturbances such as diarrhea (33%). Laboratory abnormalities were also observed, with 37% of patients experiencing neutropenia and 33% demonstrating elevated aspartate aminotransferase (AST) levels (Bristol-Myers Squibb, 2025).

Because of significant single-agent activity in patients with relapsed cHL, the drug was studied in combination with the established chemotherapy backbone of doxorubicin (Adriamycin), vinblastine, and dacarbazine (AVD) as initial therapy for the disease. This combination proved to be both tolerable and effective in treating advanced disease. This approach, referred to as Nivo-AVD, seemed to provide a clinically meaningful advantage over the previous standard, brentuximab vedotin plus AVD (BV-AVD), which is associated with higher toxicity compared with AVD alone (Lai et al., 2019; Straus et al., 2020). Although single-arm studies have shown the feasibility and early efficacy of PD-1 inhibitor–based regimens, large-scale phase III trials are necessary to confirm clinical benefit.

The SWOG S1826 trial was a randomized phase III study designed to compare the efficacy and safety of Nivo-AVD with BV-AVD in patients with newly diagnosed, advanced-stage cHL (Herrera et al., 2024). The trial enrolled patients aged 12 years and older, with both treatment arms receiving six cycles of their assigned regimens. The primary endpoint was progression-free survival (PFS). Prophylactic granulocyte colony-stimulating factor (G-CSF) was required for patients in the BV-AVD arm.

In terms of hematologic toxicity, neutropenia of any grade was more common in patients receiving Nivo-AVD, occurring in 56% (n = 272) of cases, compared with 34% (n = 160) of those treated with BV-AVD. Grade ≥ 3 neutropenia was reported in 48% (n = 232) of the Nivo-AVD group vs. 26% (n = 126) in the BV-AVD group. Notably, G-CSF was required as part of the protocol for patients receiving BV-AVD. In those receiving Nivo-AVD, it was administered at the discretion of the treating physician. Despite these differences in neutropenia rates, the incidence of infection-related complications such as febrile neutropenia, sepsis, and other infections was generally similar between the two arms. However, these events tended to be more common in older patients. Among those aged 12 to 17 years, 18% experienced complications, while 20% of patients aged 18 to 60 years and 33% of those over 60 years reported such events. This increased risk was especially pronounced in patients receiving BV-AVD (Herrera et al., 2023).

At the time of the second interim analysis, with a median follow-up of 12.1 months, the results strongly favored the Nivo-AVD regimen. One-year PFS was 94% in the Nivo-AVD arm compared with 86% in the BV-AVD group, corresponding to a hazard ratio for progression or death of 0.48 (p = .0005; Herrera et al., 2023). Nivo-AVD was also better tolerated than BV-AVD. Peripheral sensory neuropathy of any grade occurred in only 29% of those who received Nivo-AVD, as compared with 56% of those who received BV-AVD; 9% of those

in the Nivo-AVD group and 32% of those in the BV-AVD group had peripheral sensory neuropathy of grade 2 or higher. Occurrences of pneumonitis, gastritis, rash, and colitis were similar in the two groups. However, hypothyroidism and hyperthyroidism occurred more frequently after treatment in the Nivo-AVD group (in 7% and 3%, respectively) than in the BV-AVD group (in < 1% and 0%, respectively). The incidences of other adverse events, including febrile neutropenia, pneumonitis, transaminitis, and colitis, were comparable between the two treatment groups. Finally, fewer patients in the Nivo-AVD arm required consolidative radiation (0.4% vs. 0.8%), although the study protocol did not mandate radiation therapy.

Importantly, the benefit of Nivo-AVD was consistent across all analyzed subgroups. The advantage was particularly striking in patients over the age of 60, who demonstrated a PFS rate of 93% with Nivo-AVD, compared with just 64% with BV-AVD. In this older population, treatment with Nivo-AVD was also associated with lower rates of infection, peripheral neuropathy, and gastrointestinal toxicity (Rutherford et al., 2023; Cashen, 2024).

CASE STUDY CONTINUED

After completing six cycles, the patient remained asymptomatic. PET imaging demonstrated a Deauville score of 2X, consistent with a metabolic complete response. However, new lung opacities were noted. Additionally, the patient reported new gastrointestinal symptoms, including nausea, a single episode of emesis, and upper abdominal pain occurring at night. He attempted a trial of magnesium supplements and subsequently started esomeprazole, a proton pump inhibitor (PPI), for symptom relief. In addition, he reported lower gastrointestinal symptoms, including infrequent bowel movements, which he managed with over-the-counter stool softeners and laxatives. He was referred to gastroenterology for further evaluation. Esomeprazole was increased to twice daily for 2 to 4 weeks, with plans to taper to once daily and discontinue after 2 additional weeks. If symptoms did not improve, an upper endoscopy was planned.

Despite initial management, the patient continued to experience epigastric pain, nausea, vomiting, and weight loss, prompting an upper endoscopy. Upper endoscopy findings revealed a normal esophagus but also the presence of bilious gastric fluid. A large circumferential, cratered ulcer with oozing, contact bleeding, and luminal narrowing was observed at the pylorus. There was also superficial ulceration extending from the gastric pylorus to the duodenal bulb, with oozing and contact bleeding. Biopsies were taken from both sites. Histological analysis showed fibrinous inflammatory exudate and edema, with no evidence of *Helicobacter pylori* infection or history of nonsteroidal anti-inflammatory drug use. The biopsies confirmed active inflammation in the distal stomach and upper small bowel.

Given these findings, the gastrointestinal symptoms were attributed to immune-related adverse events (irAEs) from nivolumab, which can cause adverse events related to its inhibition of the PD-1/PD-L1 interaction, increasing the activity of cells which not only attack HL cells but also increase the function of these immune mediators, resulting in toxicity. The patient was started on a steroid taper to reduce inflammation and continued PPI therapy, with plans to initiate vedolizumab should it become necessary. Following this treatment, the patient reported significant improvement, with resolution of nausea, weight loss, and early satiety.

CASE DISCUSSION

This case highlights many points of consideration for the advanced practitioner (AP) managing patients receiving Nivo-AVD. Nivo-AVD is a combination of drugs that may induce irAEs that can appear nonspecific and affect multiple organ systems, which can often be confused or dismissed as other common conditions. In this patient, gastrointestinal symptoms initially appeared mild but progressed despite supportive measures, ultimately revealing significant ulcerative inflammation on endoscopy. This case identifies the critical importance of early recognition and prompt referral for specialty evaluation when irAEs are suspected. Advanced practitioners should also monitor for subtle changes in clinical status, coordinate multidisciplinary care, and implement evidence-based management strategies such as the timely use of steroids and escalation of agents like vedolizumab when indicated. Patient education,

Table 1. MASCC Risk Index

Characteristics	Score/weight
Burden of FN with no or mild symptoms	5
No hypotension (SBP > 90 mmHg)	5
No COPD	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of FN with moderate symptoms	3
Outpatient status	3
Age < 60 years of age	2

Note. FN = febrile neutropenia; SBP = systolic blood pressure; COPD = chronic obstructive pulmonary disease. Information from Wijeratne et al. (2021).

monitoring, and medication adherence are essential to prevent delays in early diagnosis to minimize complications.

Although Nivo-AVD is generally considered a well-tolerated regimen with a more favorable toxicity profile compared with BV-AVD, it brings new challenges that require close attention from APs. Immune-related adverse events such as endocrinopathies, pneumonitis, and transaminitis can be subtle and require prompt recognition and intervention. For these reasons, APs must maintain a high index of suspicion when patients present with non-specific symptoms and be prepared to initiate timely immunosuppressive therapy, including corticosteroids, when appropriate. Close monitoring, patient education, and a proactive, multidisciplinary approach are crucial for managing these potential toxicities effectively. While Nivo-AVD represents a significant advancement in frontline therapy for advanced cHL, its safe administration relies heavily on vigilant and informed clinical oversight.

TOXICITY MANAGEMENT

Neutropenia vs. Febrile Neutropenia

Neutrophils are the most abundant type of white blood cells (WBCs) and are essential to the body's immune defense. While normal ranges for WBC counts may vary slightly across clinical laboratories, the typical range in adults is approximately 4,400 to 11,000 cells/μL. Neutropenia is classified based on the absolute neutrophil count (ANC). Mild neutropenia is defined as an ANC of less than 1,500 cells/mm^3, moderate neutropenia as an ANC between 1,000 and 500 cells/mm^3, and severe neutropenia as an ANC of less than 500 cells/mm^3 (Camp-Sorrell et al., 2022). Neutropenia is a significant risk factor in patients with hematological malignancies, as they are more susceptible to bacterial and fungal infections, particularly when the ANC falls below 500 cells/μL. Prolonged neutropenia lasting more than 7 days increases the risk of bacteremia and other infections (Dash, 2024). However, in the study published by Herrera and colleagues, neutropenia occurred more frequently in the Nivo-AVD group, as patients in the BV-AVD group were routinely given G-CSF support. Despite the higher rate of neutropenia, sepsis and infections did not occur more frequently in the Nivo-AVD group compared with the BV-AVD group. Moreover, the reduced use of G-CSF in the Nivo-AVD arm was associated with less bone pain. Researchers noted that the high incidence of neutropenia without a corresponding increase in infection rates in the Nivo-AVD group was similar to what has previously been observed with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), another regimen where G-CSF prophylaxis is not routinely used (Herrera et al., 2024).

When evaluating patients for the management of febrile neutropenia, APs should consider using the Multinational Association for Supportive Care in Cancer (MASCC) risk index. This index is endorsed by the American Society of Clinical Oncology (ASCO) and the Infectious Diseases Society of America as a clinical decision-making aid. This validated assessment tool incorporates eight characteristic independent prognostic factors, each assigned a specific point value, to predict the risk of complications from neutropenic fever (> 100.5°F; Wijeratne et al., 2021). In this system, points are added according to the presence of various clinical parameters, and the total number of points indicates whether a patient is at a high or low risk of developing febrile neutropenia. A score of less than 21 identifies high-risk patients who may require inpatient management with intravenous medications, while a score of 21

Table 2. Nivolumab Adverse Event Management

Adverse event	Frequency	Category	Management considerations
Upper respiratory tract infection (including nasopharyngitis, rhinitis, sinusitis)	44%	Infection	Monitor for signs of bacterial/viral infection; treat as indicated. Hold therapy if severe.
Fatigue	39%	General	Rule out endocrine causes (hypothyroid). Supportive care, rest, and exercise.
Productive or non-productive cough	36%	Pulmonary	Evaluate for pneumonitis and rule out infection. O2 saturation, chest imaging, and pulmonary referral as needed. Steroids and consider holding nivolumab.
Diarrhea (colitis)	33%	Gastrointestinal	Grade 1: ICI continuation; adequate hydration; loperamide or diphenoxylate/atropine for 2–3 days; evaluation of lactoferrin/calprotectin levels; mesalamine and cholestyramine in addition if no improvement. Grade 2: oral steroids 1–2 mg/kg/day instead of GI motility agents; infliximab or vedolizumab is recommended if no response is observed in 2–3 days of steroid initiation. Grade 3–4: urgent GI consultation; hospitalization; IV methylprednisolone 1–2 mg/kg/day immediately; infliximab or vedolizumab in addition if no improvement.
Neutropenia	37%	Hematologic	Monitor CBC. Administer growth factor if there is febrile neutropenia.
Elevated AST	33%	Hepatic	Monitor LFTs and bilirubin. 1–2 times ULN: ICI continuation; oral steroids 1–2 mg/kg/day; mycophenolate in addition if no improvement after steroids. 3–4 times ULN: inpatient care; urgent hepatology consultation; permanent ICI discontinuation; steroid administration.

Note. AST = aspartate aminotransferase; ICIs = immune checkpoint inhibitors; O2 = oxygen; GI = gastrointestinal; IV = intravenous; CBC = complete blood count; LFTs = liver function tests; ULN = upper limit of normal. Information from Lu et al. (2020); Brahmer et al. (2021); Schneider et al. (2021); Yin et al. (2023)

or higher identifies low-risk patients who may be suitable for outpatient care (Table 1).

Low-risk features include age under 60 years, absence of hypotension (a systolic blood pressure greater than 90 mmHg), and absence of clinical symptoms such as rigors and dehydration. A thorough assessment should also include reviewing the patient's medical history, including any chronic conditions such as chronic obstructive pulmonary disease and other comorbidities. In addition, laboratory values such as hemoglobin and serum creatinine should be evaluated (Dash, 2024)

Immune-Related Adverse Events

Immune-related adverse events are toxicities caused by immune checkpoint inhibitors that are autoimmune related (Table 2). These drugs can affect various parts of the body, with the main systems involved being the skin, digestive system, endocrine system, and respiratory system. In rare cases, they can also affect the nervous system and heart (Yin et al., 2023). Such events may unpredictably impact any organ system. Symptoms typically occur within 6 months of initiating an immune checkpoint inhibitor; however, the timing of onset is highly variable and may arise at any point during therapy or even several months after treatment has been discontinued (Wright et al., 2021).

CONCLUSION

As immunotherapies become increasingly utilized to treat advanced-stage cHL, the Nivo-AVD regimen has emerged as a frontline standard of care, offering both efficacy and a more favorable toxicity profile than traditional regimens. However, the inclusion of immune checkpoint inhibitors introduces unique

challenges, particularly the risk of irAEs, which can be unpredictable and multisystemic. This article reviews the role of the AP in assessing, identifying, and managing these toxicities through vigilant monitoring, timely diagnosis, and evidence-based intervention. The presented case underscores how non-specific symptoms can hide significant irAEs and demonstrates the importance of clinical judgment, interdisciplinary collaboration, and early escalation of care. Advanced practitioners must stay informed about the evolving landscape of therapy-related toxicities to ensure safe, personalized, and effective care. Proactive involvement is crucial to optimize patient outcomes, minimize treatment-related complications, and provide comprehensive support to patients. Advanced practitioners play a critical role in the future direction of immunotherapy, which is shifting toward more personalized approaches. The use of predictive biomarkers, such as cytokine profiling, gut microbiome signatures, and genomic markers, may help identify patients at risk for irAEs, ultimately enabling safer and more individualized cancer care (Les et al., 2023). ●

Disclosure

The author has no conflicts of interest to disclose.

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