Immunotherapy-associated Autoimmune Hemolytic Anemia

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KEYWORDS

• Immunotherapy • Immune checkpoint inhibitors • Autoimmune hemolytic anemia • Immune-related adverse event

KEY POINTS

- Immune-related hematologic adverse events increasingly are reported in the literature with expanding use of immune checkpoint inhibitors.
- Diagnosis of immunotherapy-related autoimmune hemolytic anemia (ir-AIHA) requires a high index of clinical suspicion in patients who are treated with immune checkpoint inhibitors.
- Treatment of ir-AIHA can be challenging and may have an impact on the management of the underlying malignancy.

INTRODUCTION

Immunotherapy continues to play an increasingly central role in the management and treatment of cancer. Immunotherapy is a broad term that has included different classes of drugs and therapies, including immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T cell therapy. ICIs have revolutionized the therapeutic landscape of oncology and malignant hematology over the past decade, with significant improvement in survival for patients with various malignancies, including metastatic melanoma, lung cancer, renal cell carcinoma, and lymphoma. ICIs have demonstrated a strong antitumor effect through targeting of specific immune checkpoint molecules, such as programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1),

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and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), leading to up-regulation of innate immune surveillance. As the role of ICIs continues to expand, the number of recognized ICI-associated immune-related adverse events (irAEs) also has increased. The spectrum of involvement of irAEs is broad and can affect almost any organ system due to nonspecific activation of the immune system (**Fig. 1**). More recently, hematologic disorders, including red cell aplasia, cytopenias, acquired hemophilia A, cryoglobulinemia, and autoimmune hemolytic anemia (AIHA), have been recognized in the literature as rare but potentially life-threatening irAEs.[1,2]

Although CAR T cells take advantage of a patient's own T lymphocytes to treat lymphoma, leukemia, multiple myeloma, and other diseases, irAEs typically are not encountered with this modality. Despite the fact that this customized therapy entails the ex vivo transduction of a gene encoding CAR that then directs a patient's T cells against the malignant cells, extensive review of the literature and clinical experience do not reveal a consistent association between CAR T-cell therapy and irAEs, especially AIHA.[3,4] A caveat, however, is that CAR T-cell therapy is a novel therapeutic modality. It remains to be seen if additional reports of autoimmune disease, in general, and AIHAspecifically, will emerge in the future as more and more patients receive this therapy globally. Therefore, the scope of this review is focused on the description of the diagnosis, management, or prognosis of AIHA in the setting of ICI therapy.

The clinical recognition and diagnosis of immune-related hematologic adverse events (ir-h-AEs) can be particularly challenging given the high incidence of cytopenias related to cancer-directed therapies. Early identification of these clinical entities is important, however, because management typically consists of cessation of the offending ICI, with subsequent implications for the underlying malignancy, and initiation of systemic corticosteroid therapy or other immunosuppressant agents. Warm AIHA, in particular, is one of the more commonly reported ir-h-AEs.[1,5] An up-to-date, comprehensive review of the literature on ICI-associated ir-AIHA, including

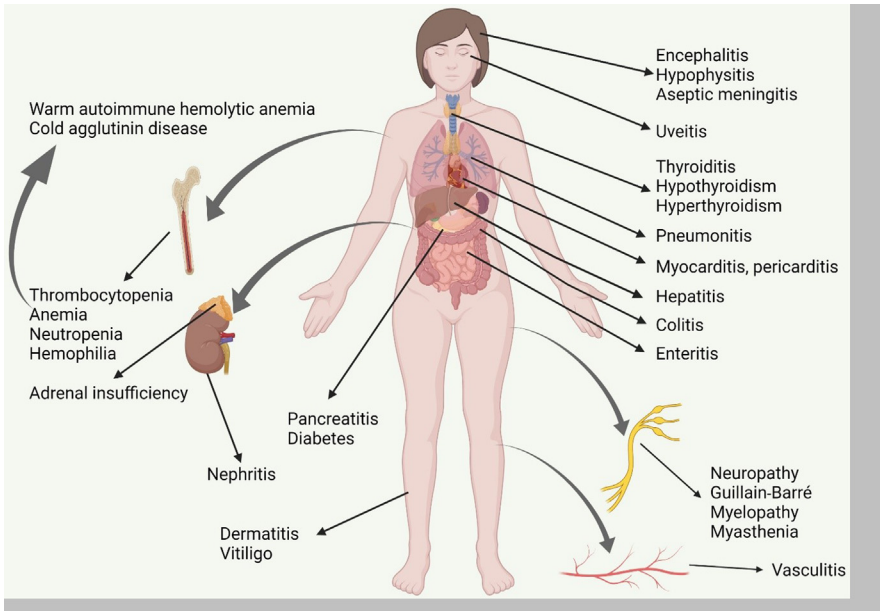

Fig. 1. Immune-related complications with ICI therapy.

epidemiology, pathophysiology, classification, clinical diagnosis, management, long-term outcomes, and risk of recurrence upon ICI rechallenge, is presented.

DESCRIPTION OF IR-AIHA EPIDEMIOLOGY

Epidemiology

AIHA is a rare disorder, with a prevalence of approximately 17 cases per 100,000 individuals.[6–9] The exact frequency of AIHA with ICI therapy is difficult to ascertain because of underdiagnosis, clinical heterogeneity, and increasing prevalence with the expansion of ICI use. Underdiagnosis likely is related to several factors.[2,10–26] For instance, in many patients receiving ICI therapy for cancer, anemia may be attributed to other concomitant risk factors like concurrent chemotherapy or radiation therapy use, nutritional deficiency in the setting of cancer cachexia, inflammation, clonal antibody production with lymphoproliferative disorders, and metastatic disease. In addition, given the rise of ICIs as effective anticancer therapies in the past decade, these medications are relatively novel. Particularly in the early days of immunotherapy in clinical practice, many oncologists and medical providers were not familiar with the whole gamut of immune-related complications associated with ICIs. A prerequisite for considering an item on the differential diagnosis list is awareness of that specific complication and its risk factors. Laboratory factors leading to underdiagnosis include the fact that 5% to 10% of patients with clear clinical evidence of AIHA have a negative direct antiglobulin test (DAT), despite using different methods, including the tube method, the more sensitive gel method, the microcolumn method, and washes with cold or low-ionic saline solutions.[27,28] Both improved recognition of AIHA as a complication of ICIs and expansion of their indications in various malignancies have driven an increase in its prevalence. Based on a review of the US Food and Drug Administration (FDA) database as reported in 2019, AIHA in the setting of ICI therapy represented 0.06% to 0.25% of all adverse events reported, occurring more commonly with PD-1 or PD-L1 targeting agents than with CTLA-4 inhibitors.[2] The underlying cancer types mainly were melanoma (41%), non–small cell lung cancer (26%), renal cell carcinoma, Hodgkin lymphoma, and skin cancers.[2] Most cases were IgG-positive warm AIHA, and cold agglutinin disease (CAD) was diagnosed less frequently.[2]

Based on the authors' review of the literature, various ICI agents have been associated with AIHA. The agents reported most commonly associated with AIHA include pembrolizumab, nivolumab monotherapy, ipilimumab and nivolumab combination therapy, ipilimumab monotherapy, and atezolizumab.[1,2,5,20,29] Because the literature search included mostly case series and case reports, it is difficult to ascertain the true prevalence or relative risk of AIHA with the use of different ICI agents. **Table 1** summarizes the larger case series of AIHA with ICI therapy reported in the literature. Although most diagnoses of AIHA were made within 100 days of initiation of therapy with ICIs, cases were reported as early as after 1 cycle and as late as after 39 cycles of therapy.[1,2]

Etiology and Classification

The pathophysiologic premise for ICI–associated ir-AIHA most likely is related to increased immune surveillance. This mechanism of action should be distinguished from other drug-induced AIHAs, where 2 pathophysiologic processes may contribute to hemolysis: (1) binding of autoantibodies to red blood cells (RBCs) only in the presence of the drug through a hapten mechanism and (2) complement-mediated destruction in the presence of the drug through a ternary complex mechanism.[30] Warm AIHA is characterized by antibody-dependent cytotoxicity, mediated by cytotoxic $CD8^+$ T cells and natural killer cells, because the main site of destruction is of RBCs is the

Table 1
Summary of published case series of immune-related auto-immune hemolytic anemia

Case Series (Source)	Number of Patients (n)	Malignancies (n or %)	ICI Used (n or %)	Median Number of Cycles (Range)	Disposition of ICI (% of n)	Treatment of ir-AIHA (n or %)	Outcome of ir-AIHA (n or %)	Disposition of ICI after ir-AIHA resolved (n or %)	ICI Continued Outcomes (n or %)	ICI Rechallenged Outcomes (n or %)
Tanios et al, 2018 (FDA database)	68	Melanoma (32) NSCLC (24) HL (2) RCC (2) Breast (2) Ovarian (1) Not reported/ other (5)	Nivolumab (31) Pembrolizumab (13) Ipilimumab/ Nivolumab (12) Ipilimumab (7) Atezolizumab (5)	NA	NA	NA	NA	NA	NA	NA
Tanios et al, 2018 (Literature review)	12	NSCLC (6) Melanoma (4) HL (1) Urothelial (1)	Nivolumab (8) Pembrolizumab (2) Ipilimumab/ Nivolumab (2)	5.5 (1-39)	NA	Steroids (8) Steroids plus rituximab (2) Steroids plus IVIG (2) Rituximab (1)	CR (9) PR (1) NR (2)	NA	NA	NA
Delanoy et al, 2019 (French pharmaco-vigilance databases)	9	Melanoma (4) NSCLC (3) RCC (2)	Nivolumab (8) Pembrolizumab (1)	2 (1-21)	Held (100%)	Steroids (4) Steroids plus rituximab (5)	CR (6) NR (3)	Rechallenged (1) Discontinued (8)	NA	No recurrent irAE (1)
Leaf et al, 2019 (Multi-center case series)	14	Melanoma (9) NSCLC (3) Colorectal (1) AML (1)	Pembrolizumab (6) Ipilimumab/ Nivolumab (4) Nivolumab (3) Ipilimumab (1)	3.5 (1-12)	Held (79%)	Steroids (12) Steroids plus rituximab (1) Steroids plus IVIG (1)	CR (12) PR (2)	Continued (3) Rechallenged (4) Discontinued (7)	CR, Recurrent ir-AIHA (1) PR, recurrent ir-AIHA (1) CR, recurrent non-heme irAE (1)	No recurrent irAE (4)

Kramer et al, 2021 (Multi-center case series)	8	Not reported	Nivolumab (3) Ipilimumab/ Nivolumab (2) Pembrolizumab (1) Ipilimumab (1) Pembrolizumab/ Ipilimumab (1)	2 (1-10)	Held (78%)	Steroids (4) Steroids plus IVIG (1) Steroids plus IVIG and rituximab (1) Steroids plus alemtuzumab (1) Not reported (1)	CR (5) PR (3)	Continued (1) Rechallenged (2) Discontinued (5)	PR, no recurrent irAE (1)	Recurrent ir-AIHA (1) Recurrent non-heme irAE (1)
Saliba et al, 2021 (Single-center case series)	7	NSCLC (3) Melanoma (2) Pancreatic (1) Esophageal (1)	Pembrolizumab (7)	5 (3-15)	Held (86%)	Steroids (6) Steroids plus IVIG (1)	CR (5) PR (3) NR (2)	Continued (1) Rechallenged (3) Discontinued (3)	CR, no recurrent irAE (1)	Recurrent ir-AIHA (3)
Aggregate of all Case Series	118	Melanoma (49%) NSCLC (37%) HL/AML (4%) GU (4%) GI (3%) Breast (2%) Ovarian (1%)	Nivolumab (45%) Pembrolizumab (25%) Ipilimumab/ Nivolumab (17%) Ipilimumab (8%) Atezolizumab (4%) Other (1%)	3 (1-39)[a]	Held (87%)	Steroids (69%) Steroids plus rituximab (16%) Steroids plus IVIG (10%) Other (6%)	CR (68%) PR (18%) NR (7%)	Continued (13%) Rechallenged (26%) Discontinued (61%)	Recurrent irAE (60%) No recurrent irAE (40%)	Recurrent irAE (50%) No recurrent irAE (50%)

[a] Available in 44 patients

spleen and the lymphoid organs.[31] Other pathophysiologic mechanisms involve imbalance of $CD4^+$ regulatory T cells and autoreactive cellular effectors, including activated macrophages via Fc receptor phagocytosis of RBCs opsonized by autoantibodies and complement and T cells.[8]

AIHA can be encountered in association with B-cell malignancies, autoimmune diseases, or drugs.[32] Although drug-induced AIHA is uncommon, the list of drugs that may cause it is expanding.[33] Drug-related antibodies may be drug-independent or drug-dependent. Drug-independent antibodies can be detected in vitro in the absence of the implicated drug. Drugs commonly associated with AIHA mediated by drug-independent antibodies include methyldopa and fludarabine. Drug-dependent antibodies are directed against epitopes on (1) the drug or its metabolites, known as a hapten reaction, or (2) a combination of the drug and the RBC membrane. The drug binds to the RBC surface and becomes part of the antigen. Therefore, drug-dependent antibodies only react in vitro in the presence of the drug. Hapten reactions can be subdivided further into several types. The penicillin type involves a drug that remains on the RBC membrane as a prerequisite for antibody binding. Cephalosporins and penicillin typically cause hemolysis via this mechanism. The immune complex type involves the formation of immune complexes that bind the RBCs then cause complement activation. The passive adsorption type is associated with the administration of antibody preparations like intravenous immune globulin (IVIG). The preparations contain immune complex–type alloantibodies that can react with the recipient's RBC antigens causing alloimmune hemolysis.

Although the precise pathophysiology of AIHA associated with ICI therapy has not been studied extensively and remains unclear, it is believed that the process is related to immunologic dysregulation. When engaged by antibody cross-linking or binding to B7, CTLA-4 dampens the immune response mainly by inhibiting T-cell activation (1) regardless of apoptotic signals and (2) through the restriction of T-cell transition from the G1 phase to the S phase in the cell cycle.[34] PD-1 and its ligands PD-L1 and programmed death ligand 2 (PD-L2) maintain peripheral immune tolerance.[35] They mediate quiescence of mature autoreactive T cells that have escaped central tolerance in the thymus.[35] A tumor overexpressing the function of PD-L1 protects itself from cell killing mediated by $CD8^+$ cytotoxic T cells.[36,37] To counteract this immune tolerance, B7-1, a protein expressed on activated T cells and other antigen-presenting cells, causes down-regulation of the effector T-cell activation by interacting with the PD-L1 on tumor cells.[37] Inhibiting these endogenous immune checkpoints unleashes the immune response against tumors and occasionally against normal cells. Whether autoreactive T cells or autoreactive antibodies are the main driver of many irAEs remains unknown and may not be consistent across different complications. AIHA with ICI is unlikely to be mediated by adsorption to RBC membrane and development of autoantibodies. It also is unlikely that there is cross-reactivity between the drug neoantigen and a red cell antigen. The more likely explanation revolves around immune system activation with subsequent autoantibody formation, blunting of the activity of regulatory T cells, and awakening of quiescent T-cell clones (**Fig. 2**). In a recent publication, among the 127 patients who had either DAT or alloantibody testing prior to ICI initiation, there was no association between DAT positivity before ICI and development of irAEs.[38] Further research is needed to elucidate the pathophysiologic mechanisms underpinning the development of ir-AIHA.

AIHA can be (1) primary, when no association with a secondary cause can be established, or (2) secondary, when an underlying disorder is suspected to be driving the hemolytic process. Secondary causes include lymphoproliferative disorders, autoimmune disease, medications (including antimicrobial agents, such as piperacillin, and

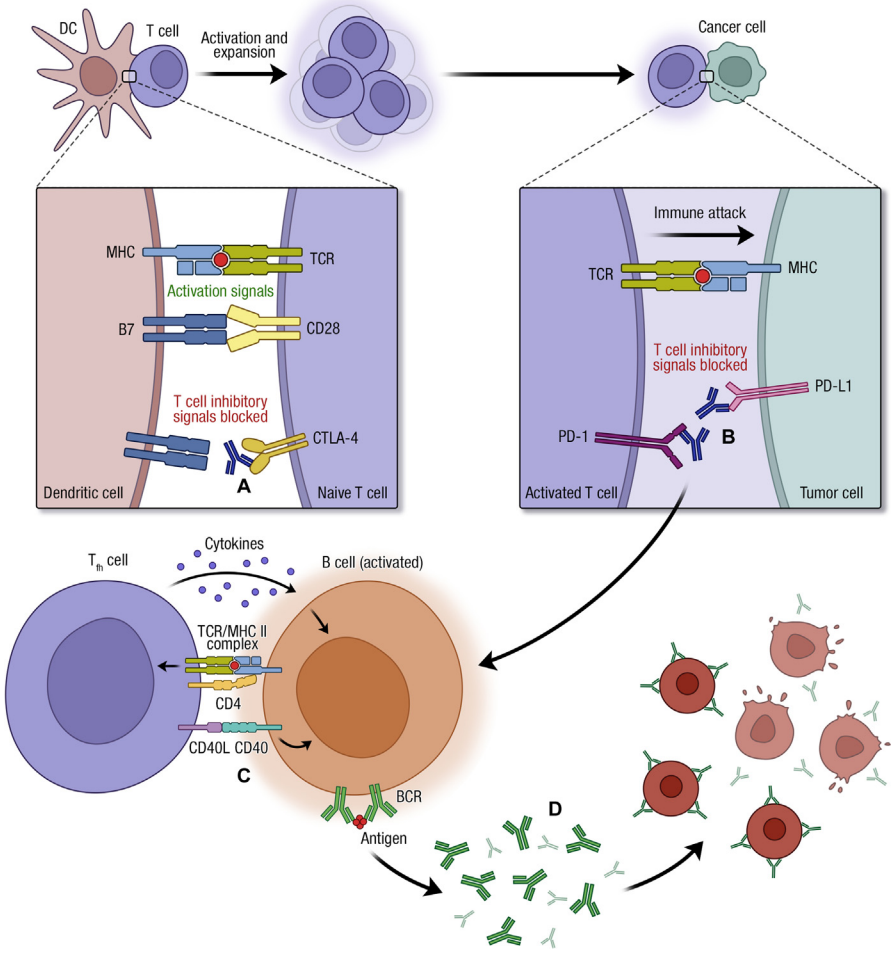

Fig. 2. Proposed mechanisms of warm AIHA due to ICI therapy. Immune checkpoint inhibitors inhibit T-cell–negative costimulation to unleash antitumor T-cell responses directed against tumor antigens. CTLA-4 inhibitors, such as ipilimumab, are anti–CTLA-4 antibodies that block the interaction between CTLA4 and B7, facilitating the activation of T cells (*A*). The interaction between PD-1, expressed on activated T cells, and PD-L1, expressed on tumor cells, dampens the function of T cells. PD-1 inhibitors, such as pembrolizumab and nivolumab, and PD-L1 inhibitors, such as atezolizumab, block the interaction between PD-1 and PD-L1, facilitating the activation of T cells (*B*). T-cell–mediated regulation of the humoral immune system is believed to have an important role in loss of self-tolerance in ir-AIHA. Activated helper T cells stimulate B cells (*C*) to secrete autoantibodies directed against RBCs (*D*). The interaction between the RBC antigen-binding B cell with a helper T cell leads to the expression of CD40L on the helper T cell (T_{fh}), and secretion of interleukins stimulate further proliferation of B cells and differentiation into auto-antibody–secreting plasma cells. Blue antibodies denote pharmacologic monoclonal antibodies acting as ICIs. Green antibodies denote autoantibodies produced by activate B cells. BCR, B-cell receptor; DC, dendritic cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

chemotherapy agents, such as fludarabine and oxaliplatin), infection, or other malignancies.[39–41] Warm AIHA and cold AIHA, including CAD, have been reported with ICI therapy.[1,17]

Diagnosis

A diagnosis of AIHA generally is suspected based on clinical findings and confirmed with laboratory evaluation.[42] Common clinical symptoms warranting investigation for AIHA generally are nonspecific and include fatigue, dyspnea, and lightheadedness, with the severity of symptoms paralleling the degree of anemia and the rapidity of its onset. Physical examination can reveal skin and conjunctival pallor, jaundice, tachycardia, and potentially splenomegaly, particularly in patients with an underlying lymphoproliferative disorder. Once hemolytic anemia is suspected, laboratory evaluation must be performed in a timely manner. Common laboratory features of AIHA include a low hemoglobin, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase, elevated reticulocytes, features of hemolysis seen on peripheral blood smear (ie, spherocytes or microspherocytes for warm AIHA, red cell agglutination for CAD, and reticulocytes), and commonly a positive DAT.

A diagnosis of ir-AIHA is seen within the greater context of the many irAEs. Clinicians should maintain a high index of clinical suspicion when treating any patient with an ICI and a low threshold for initiating diagnostic evaluation for irAEs.[42] This also applies to other ir-h-AEs, and may be even more important given the commonality of cytopenias in patients treated with ICIs due to the underlying malignancy, cancer-directed therapies, or a combination of both. The most commonly associated ICIs were seen with atezolizumab (anti–PD-L1) and nivolumab (anti–PD-1), at 0.25% and 0.21% of all irAEs reported, respectively. In comparison, the proportion of ir-AIHA in patients treated with ipilimumab (anti–CTLA-4) was only 0.06% of all adverse events—irAEs and otherwise—reported.[2]

Diagnostic criteria for ir-AIHA previously have been proposed as (1) an abrupt decrease in hemoglobin by greater than 2 g/dL; (2) laboratory features suggestive of hemolysis, including elevated lactate dehydrogenase and low haptoglobin; (3) temporal association of AIHA after initiation of ICI; (4) exclusion of other causes of acute anemia; and (5) ICI therapy, considered the most likely etiology of AIHA.[20] There appears to be a relatively high prevalence of DAT-negative AIHA in patients diagnosed with ir-AIHA compared with nonICI-associated ir-AIHA, reported as high as 27% to 38% in 1 aggregate cohort review of 31 cases.[20] The proposed reason for this discrepancy could be antibody-independent mechanisms RBC destruction, such as ICI-induced proinflammatory states leading to direct macrophage phagocytosis of RBCs, in a fashion similar to hemophagocytic lymphohistiocytosis. Further studies are needed, however, to investigate for any differences in pathophysiology of DAT-positive and DAT-negative ir-AIHA. None of the patients identified in that particular study underwent enhanced DAT testing, so the true prevalence of DAT-negative ir-AIHA may be lower and closer to the prevalence of that seen in general AIHA.[20]

In CAD, the primary clinical symptom, in addition to those discussed previously related to hemolysis, is cold-induced acrocyanosis, Raynaud phenomenon, or livedo reticularis.[43] Initial evaluation for CAD is similar to that detailed previously for warm AIHA. DAT is positive, however, for the complement component C3b and generally negative for immunoglobulin. Diagnostic criteria for ir-CAD are even more difficult to delineate than those for warm ir-AIHA, primarily due to the paucity of reported cases. Given this, the authors recommend using similar diagnostic criteria to those for non–ICI-associated CAD, with the important additional history of exposure to an ICI as a required criterion.

Treatment

Management of warm AIHA is centered around decreasing the production of IgG autoantibodies with early use of prednisone as first-line therapy.[44] The administration route is dependent on the severity of presentation, with intravenous methylprednisolone reserved for acute presentations with or without hemodynamic instability or inability to tolerate medications enterally; otherwise, oral prednisone, 0.5 mg/kg to 2 mg/kg with a prolonged taper, can be used.[42,45,46] The initial response rate is reported as approximately 70% to 80%,[45] with up to 20% to 40% of patients achieving a durable remission.[47] The remainder subsequently have a chronic, relapsing course requiring subsequent lines of therapy.[45,48] In particularly severe initial presentations of warm AIHA, IVIG also can be used as adjunctive therapy.[49]

Historically, splenectomy has been considered second-line therapy for cases that did not respond to steroids[50] but is associated with poor long-term cure rates of only approximately 20% and increased risks of complications, including infections secondary to encapsulated bacteria in up to 3.3% to 5.0% of patients.[51,52] Rituximab has emerged more recently as the preferred agent for second-line treatment in these patients.[32,53,54] In relapsed/refractory warm AIHA previously treated with steroids, the overall response rate with rituximab is approximately 70% to 80%, with a median duration of response of 1 year to 2 years.[55,56] Most patients respond within 4 weeks after initiation of rituximab.[55,56] Rituximab also has been investigated as first-line therapy in warm AIHA in prospective randomized phase III trials as combination therapy with steroids.[57,58] Both these aforementioned studies showed that addition of rituximab to steroid therapy resulted in nearly identical outcomes with a significantly higher overall response rate (75% vs 31%–36%,), complete response (34% vs 16%), and longer duration of response.[57,58] Given these rates, some hematologists consider using rituximab in the first-line setting for management of warm AIHA. Given its significant side-effect profile, however, notably risk of infection with hypogammaglobulinemia; neutropenia; and risk of reactivation of underlying infections, such as hepatitis B, HIV, and tuberculosis, rituximab—particularly in an often already immunocompromised group of patients—still the is most used in the second-line setting.[46] The most common dose of rituximab used in standard practice is 375 mg/m^2 per week for 4 weeks. Other doses, including 1 g every 2 weeks for 2 doses and 100 mg per week for 4 weeks, have been used with relatively similar response rates, although direct comparisons have not been made.[46]

In particularly severe or refractory cases of warm AIHA, other immunosuppressive therapies have been studied, such as azathioprine, cyclophosphamide, mycophenolate mofetil, and cyclosporine.[59–62] Data assessing overall response rate have been limited, however, to retrospective studies, case series, and case reports. Overall response to those agents, with the caveat of selection for a more refractory subset of warm AIHA, is relatively poor, with a reported overall response rate of approximately 30% to 50%.[59–62] Novel therapeutic agents, such as fostamatinib (spleen tyrosine kinase inhibitor), daratumumab (anti-CD38 antibody), ibrutinib (Bruton tyrosine kinase inhibitor), and alemtuzumab (anti-CD52 antibody), are actively being investigated for potential roles in refractory cases of warm AIHA, with several randomized clinical trials ongoing at this time.[27,63,64]

The treatment of CAD differs greatly from that of warm AIHA. This distinction underscores the importance of establishing a correct clinical diagnosis prior to initiation of first-line therapies. Current therapies for CAD rely on the 2 major bedrocks of the pathogenesis: (1) clonal B-cell lymphoproliferation and (2) complement-mediated hemolysis. The role of steroids is limited in CAD, with a reported remission rate of less than

20% and requirement for high maintenance doses to sustain remission in the few patients who respond.[43,46,65] The role of splenectomy also is limited due to the predominant location of extravascular hemolysis in CAD being the liver.[66,67] B-cell–directed therapies, such as rituximab, have shown promise in several observation studies and a few prospective, nonrandomized trials.[43,68] Given this, rituximab is well-established as first-line therapy in CAD, with a standard dose of 375 mg/m^2 per week for 4 weeks.[54,63] In addition, in the setting of recurrence, retreatment often succeeds in achieving a second response.[69] A prospective trial investigated the addition of bendamustine to rituximab as first-line treatment of CAD and showed an overall response rate of 71%, with a prolonged median response duration of greater than 88 months, sustained for longer than 5 years in 77% of responders, although there was a moderate incidence of grade 3 to grade 4 toxicities noted.[43,70] Given these results, it is reasonable to add bendamustine to patients who do not show response to rituximab early in the treatment course.

The management of ir-AIHA has not been well established, mostly due to the overall rarity of this clinical entity. Therefore, treatment is based primarily on expert guidelines, case series, and reviews of the literature.[42] Glucocorticoids, such as intravenous methylprednisolone and oral prednisone (depending on the severity of the initial presentation), appear to be reasonable first-line options due to the presumed pathophysiology of warm ir-AIHA, as described previously, with the goals of decreasing production of IgG autoantibodies and slowing the rate of RBC destruction. In addition, cessation of the ICI generally is recommended in the setting of active warm ir-AIHA. In patients who do not respond to initial treatment with glucocorticoids, use of rituximab at a similar dose used for treatment of non–ICI-associated warm AIHA is the recommended second-line therapy. Review of the reported cases available in the literature shows an overall response rate of approximately 57% to 75% of patients treated with steroids with or without rituximab.[43,70] In cases of warm ir-AIHA refractory to steroids and rituximab, other immunosuppressive agents used in warm AIHA can be considered, although there are no studies to suggest a preferred agent and clinicians would need to decide on a case-by-case basis. Treatment of ICI-associated immune-related CAD (ir-CAD) is even less well defined, given the paucity of published cases. The authors' recommendation is to use a treatment algorithm similar to that of non–ICI-associated CAD, described previously for ir-CAD. Additionally, for CAD associated with ICI, caution must be exercised to avoid adding an alkylating agent, such as bendamustine, if other chemotherapy drugs are administered concomitantly—especially in patients with cytopenias related to the myelosuppressive effects of cytotoxic therapy. For patients with responding or stable cancer while CAD is progressing, a short interruption or pause in other chemotherapeutic agents is reasonable while the hemolysis is addressed. A proposed algorithm for the management of ir-AIHA is presented in Fig. 3.

Prognosis

The overall initial response rate of patients with ir-AIHA is reported to be approximately 57% to 75% with use of first-line and second-line agents, including steroids and rituximab, acknowledging the limited number of cases and lack of substantial follow-up.[2,5,20] Rechallenging with an ICI in patients with previous but resolved irAE has been discussed in prior studies, with review of the recent literature suggesting retrialing ICIs as long as patients are monitored closely.[71] In cases of ir-AIHA, in particular, Hwang and colleagues[15] reported a case of a patient who developed ir-AIHA in the setting of metastatic melanoma treated with ICI and who subsequently was rechallenged with ICI therapy on 2 separate occasions and developed recurrence of ir-

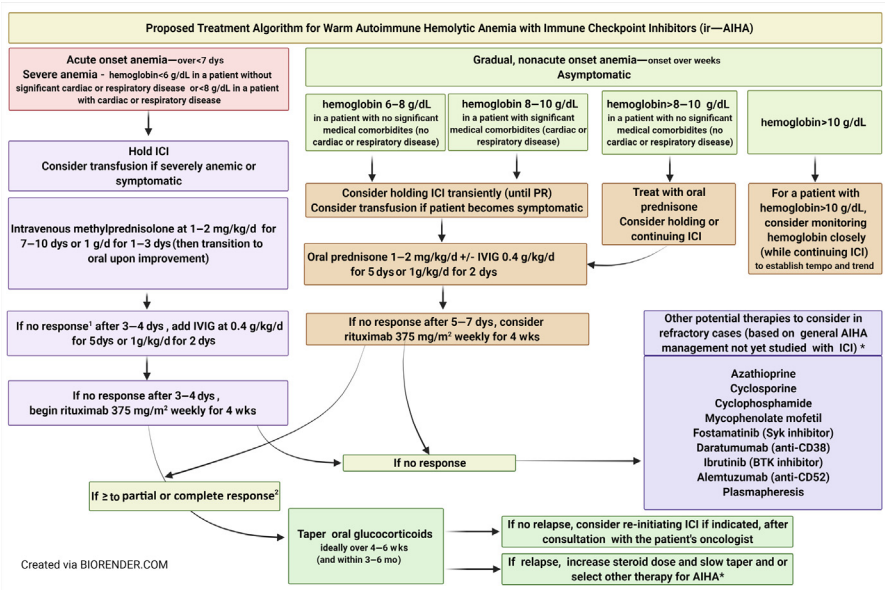

Fig. 3. Proposed treatment algorithm for AIHA with ICIs. (1) Response defined as an increase in hemoglobin of 1 g/dL or greater without dependence of blood transfusions. (2) Achieving partial response (PR) defined as a hemoglobin greater than 10 g/dL but less than 12 g/dL and 2 g/dL above the nadir without blood transfusion. (3) Complete response defined as a hemoglobin of greater than or equal to 12 g/dL and 2 g/dL above the nadir without blood transfusion. BTK, Bruton tyrosine kinase. Created with BioRender.com.

AIHA both times. Leaf and colleagues[20] reported, however, that of the 14 patients in their study, 4 (29%) were rechallenged with ICI, with none having recurrence of AIHA, and 3 (21%) were continued on ICI throughout initial ir-AIHA diagnosis, all 3 of whom had subsequent recurrence of ir-AIHA or other irAE (hepatitis, acute kidney injury, or ICI-associated immune-related *immune* thrombocytopenic purpura.[20] In a literature review by Delanoy and colleagues,[5] only 1 of the 9 patients with ir-AIHA reported underwent rechallenge with ICI, and that patient did not experience recurrence of AIHA. Overall, it appears that rechallenge with ICI in patients with resolved ir-AIHA can be trialed, particularly if alternative cancer-directed therapies are suboptimal to treatment with ICI, with strong recommendations for close and frequent monitoring of clinical and laboratory parameters. In addition, alternative etiologies of both hemolytic and nonhemolytic anemia must be considered when monitoring for recurrence, particularly if there are concurrently administered cytotoxic medications, evidence of metastatic bone marrow involvement, or secondary malignancies involving the bone marrow, such as therapy-related myeloid neoplasms.

SUMMARY

Immunotherapy has changed the therapeutic landscape of malignant hematology and oncology. As immunotherapy—ICIs, in particular—become used more widely, the number of reported irAEs also is increasing. A growing number of ir-h-AEs, including warm ir-AIHA and ir-CAD, are recognized as clinically important entities with challenging diagnostic and management decisions in practice. This review

provides a comprehensive look into the current understanding of pathophysiology, epidemiology, and diagnostic approach to ir-AIHA. In addition, currently published cohorts of patients with warm ir-AIHA and ir-CAD are summarized, including details of pertinent patient characteristics, timing of onset to ir-AIHA after ICI initiation, treatment of ir-AIHA, and long-term outcomes of both the irAE and the patient's underlying malignancy. Finally, the topic of rechallenging ICI therapy in patients with resolved ir-AIHA is touched on and an algorithm in the management of these patients proposed.

CLINICS CARE POINTS

- Immunotherapy including the use of ICIs are becoming more popular in the management of a greater number of malignancies.
- Reported irAEs including Hematologic complications such ICI-associated warm ir-AIHA and ir-CAD, are more frequent, and present challenging diagnostic and management decisions in practice.
- Clinicians must maintain a high index of suspicion for these complications.
- The severity and acuity of the anemia must be taken into consideration in the management of ir-AIHA.
- Standard front-line therapy for ir-AIHA includes the use of steroids upfront, as well as consideration of the addition of Rituximab or IVIG. There is no consensus in the management of refractory or relapsed disease.
- Decisions regarding the disposition of ICI use is not straightforward, however current recommendations include discontinuation in the context of severe anemia.
- Rechallenging patients with an ICI once the anemia is corrected remains a point of debate and must be discussed within the context of the patient's underlying malignancy and therapeutic options together with oncology.

DISCLOSURES

No conflicts of interest or disclosures to declare.

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