







## CLINICAL GUIDELINE

**Clinical diagnosis and treatment recommendations for immune checkpoint inhibitor-related hematological adverse events**

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**Introduction**

The Nobel Prize in Physiology or Medicine 2018 was awarded to two scientists who discovered outstanding cancer therapy by inhibition of negative immune regulations. In

**Abstract**

Immune checkpoint inhibitors (ICIs) are able to reactivate the immune system, thereby enhancing the anti-tumor effects. However, over-activated T cells may induce immune-related adverse events (irAEs). Hematological irAEs are rarely reported which mainly represent monolineage cytopenia or pancytopenia, including autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), neutropenia and aplastic anemia, sometimes even life-threatening diseases such as hemophagocytic lymphohistiocytosis. Here, the clinical manifestations of hematological irAEs are summarized and recommendations for diagnosis and treatment proposed.

**Key points****Significant findings of the study**

- Hematological immune-related adverse events (irAEs) caused by checkpoint inhibitors are rare and may sometimes be life-threatening. This study summarizes the manifestations of hematological irAEs and proposes preliminary recommendations for diagnosis and treatment.

**What this study adds**

- Much still remains unknown regarding hematological irAEs caused by checkpoint inhibitors. This study delineates the overview of hematological irAEs, and provides practical treatment suggestions, in particular addressing the issue of rechallenge.

fact, the exploration of anti-tumor immunotherapy has been carried out for decades. In particular, the understanding of the interaction between a tumor and the immune system has grown rapidly over the last decade. Tumor cells activate

immune checkpoints such as molecular programmed death receptor-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) signaling pathways to inhibit T lymphocyte activation and thus escape from immune surveillance, known as “immune brake”.<sup>1</sup> Immune checkpoint inhibitors (ICIs) reactivate T lymphocytes to recognize cancer cells by blocking CTLA-4 or PD-1. Therefore, immunotherapy has become a novel strategy for numerous types of cancer. However, resulting immune-related adverse effects (irAEs) have also been reported.<sup>2</sup> They mainly include immune system organs, skin, lungs, endocrine glands and gastrointestinal tract, etc.

Hematological AEs (hema-AEs) caused by ICIs are rare, with few cases reported. A meta-analysis of 9324 patients indicated the incidence of anemia, neutropenia, and thrombocytopenia was 9.8%, 0.94%, and 2.8%, respectively.<sup>3</sup> Most of the hema-AEs manifested as monolineage cytopenia, or bilineage cytopenia such as thrombocytopenia with neutropenia, and even pancytopenia such as aplastic anemia. Other rare AEs include acquired hemophilia A,<sup>4</sup> eosinophilia,<sup>5</sup> large granular lymphocytosis (LGL), even life-threatening diseases such as hemophagocytic lymphohistiocytosis.<sup>7</sup> This article aims to provide a comprehensive description of hematological irAEs in cancer patients treated with ICIs and suggest preliminary treatment recommendations.

### Autoimmune hemolytic anemia (AIHA)

AIHA is the most commonly reported hema-AE. A total of 68 cases have so far been studied with a similar ratio of men to women. The underlying diseases are mainly melanoma (41%), non-small cell lung cancer (NSCLC, 26%), and others including kidney cancer, Hodgkin's lymphoma or skin cancers. The reported cases were mainly from North America (49%) and Europe (34%), with a few from Asia (10%) and Australia (7%). A total of 60% of patients were treated with a single anti-PD-1 monoclonal antibody (mAb), most of which were nivolumab; 19% with anti-CTLA-4, 16% with combined, and 4% with anti-PD-L1 mAb.<sup>8</sup>

### Clinical manifestations

The median time to onset of AIHA was approximately 50 days after administration of ICIs, while a few cases occurred more than 180 days, among whom four patients had concurrent thrombocytopenia, the other four had endocrine abnormalities including thyroiditis, adrenal insufficiency or hypophysitis, and three had gastrointestinal AE such as colitis or hepatitis. With regard to the laboratory tests, the Coombs test was positive, most of which were IgG, and a few with C3 alone. Most were warm AIHA, and very few were cold agglutinin.<sup>8</sup>

### Diagnosis and differential diagnoses

A positive direct agglutinin test (Coombs) is the diagnostic criteria for AIHA. Other hemolytic evidence includes elevated reticulocyte count, unconjugated bilirubin and serum lactate dehydrogenase, etc. Anemia is not rare in cancer patients, which could be related to many factors including marrow suppression after chemotherapy, tumor progression or anemia of chronic disease (ACD), etc. As ICI-related AIHA is rare, it is necessary to identify other causes. Reticulocytes, serum iron and ferritin, serum folic acid, vitamin B12 are basic tests. Bone marrow biopsy is not required unless it is to differentiate from other conditions such as myelodysplastic syndrome, marrow metastasis of tumor cells or rare pure red cell aplastic anemia (PRCA).

### Treatment

More than 80% of patients developed grade 3–4 anemia and required red blood cell transfusion. The associated mortality rate reached approximately 15% due to delayed diagnosis and organ failure caused by severe anemia. Once diagnosed, treatment with corticosteroids is recommended with an initial dose of prednisone commencing at 1.5 mg to 2 mg/kg per day which should be reduced after full dose use of 2–4 weeks. The duration of treatment is approximately three months. In some patients, AIHA relapses after premature cessation of steroids, but reapplication is still effective. Although AIHA presents a benign process as a whole, ICIs should be discontinued during the administration of steroids.<sup>8–14</sup> Other immune suppressor therapies are not recommended because most cases of AIHA recover with single steroid treatment.

The rechallenge of ICIs after AIHA has improved or is stable remains inconclusive. It has been reported that a patient with Hodgkin's lymphoma was treated with two doses of nivolumab. The PD-1 mAb was discontinued because AIHA occurred. Steroids were then given at a dose of 2 mg/kg and tapered for three months. A very good response was achieved to PD-1 mAb but there was tumor progression. Nivolumab was then administered in six doses without any recurrent hemolysis.<sup>14</sup> Therefore, it is possible to rechallenge ICIs based on tumor response and control of hemolysis.

### Immune thrombocytopenia (ITP)

The second most common hema-AE is immune thrombocytopenia (ITP). ITP does not have a specific diagnostic indicator in patients with cancer, and mimics other types of thrombocytopenia (TCP) caused by infection, tumor progression, or other chemo-drugs even combined with ICIs. There are currently no predictive biomarkers identified for ITP, but the positive auto-antibodies may be associated with the development of ITP before ICI treatment.<sup>15</sup>

Among the 57 ICI-related ITP patients in the report by Davis *et al.* melanoma and NSCLC were still the most frequently reported. Cases were primarily from North America (53%), followed by those in Asia (33%) and Europe (14%). Among them, 65% of patients were treated with anti-PD-1 mAb alone; 16% with anti-CTLA-4, 18% with combined, and 2% with anti-PD-L1 mAb.<sup>8</sup>

### Clinical manifestations

ITPs occurred at a median of 41 days (range 14–321 days), generally within the first 12 weeks of ICI initiation. Seven were comorbid with AEs in the digestive system, four with other blood AEs, and a few with skin and endocrine abnormalities. The grade of thrombocytopenia was based on the Common Terminology Criteria for Adverse Events (CTCAE).

Most cases had severe TCP. Usually not until grade 4 TCP develops can it cause severe spontaneous bleeding, such as the skin mucosa which can be life-threatening.<sup>8,9</sup> Mortality was reported in 11% of cases in the report by Delyon *et al.*<sup>4</sup>

### Diagnosis and differential diagnoses

Because alternative causes for the TCP are common in cancer patients, there is a reasonable risk that ir-TCP may be under-recognized. In addition to routine blood tests and differential counting of peripheral blood, autoantibody detection is a testament to the diagnosis of ITP, but it is not indispensable. Although bone marrow aspiration is not required for primary ITP, marrow cytology and biopsy are needed in TCP of irAEs to exclude hypocellularity or peripheral exhaustion of platelets. Most ITPs are characterized by increased counts of marrow megakaryocytes, or may be substantially normal, and dominated by immature megakaryocytes. In addition, infection-related TCP should be considered as pathogens include bacteria EBV, cytomegalovirus (CMV), parvovirus B19, hepatitis virus, HIV, etc.

### Treatment

A grade 1 TCP or PLT count below 50% of the baseline value requires close monitoring at least twice a week, and suspension of ICIs is unnecessary. Grade 2 TCP warrants the transient withdrawal of ICIs and the application of corticosteroids which are tapered gradually after using them for 2–4 weeks. With regard to grade 3 or 4 TCP, in addition to discontinuing the immunotherapy, prednisone or methylprednisolone 1 to 2 mg/kg should be started as soon as possible, with or without IVIG, which is similar to the treatment of adult primary ITP. If the PLT count responses quickly, the steroids can be gradually reduced after a standard administration of two to four weeks. If first-line treatment fails, rituximab, splenectomy, thrombopoietin receptor

agonists or second-line immunosuppressive drugs such as cyclosporine, azathioprine, etc can be considered.<sup>8,9,15–17</sup>

Although grade 1 or 2 TCP may recover spontaneously after transient or permanent discontinuation of ICIs, a recently published meta-analysis showed that 78% of ITP was grade 4 TCP. All patients were treated with corticosteroids, and two/three concurrently received IVIG, yet 22% of patients did not respond to these treatments and switched to a thrombopoietin receptor agonist or rituximab. The rechallenge of ICIs after the remission of TCP is still inconclusive. In three readministered cases, one patient had a recurrence of thrombocytopenia, so the risk and benefit of rechallenge need to be fully balanced.<sup>8,9,15</sup>

### Neutropenia

Neutropenia is a rare irAE, with up to nine cases reported in a meta-analyses, among which ipilimumab was the most commonly used, followed by nivolumab and pembrolizumab.<sup>9</sup> The underlying cancers were melanoma, NSCLC and prostate cancer. Due to the lack of characteristic diagnostic indicators for ICI-related neutropenia, it is necessary to recognize other causes including viral infections, marrow suppression caused by other chemotherapeutic drugs, etc. If ICIs alone are used, the possibility of other drugs causing neutropenia can be ruled out.<sup>9</sup>

### Clinical manifestations

Neutropenia occurred at the median time of the third cycle after administration, all cases of which were diagnosed as grade 3 to 4. Approximately 20% to 30% of patients with neutropenia were combined with other irAEs such as rash, digestive tract reactions, and other hematological abnormalities. Bacterial or fungal infections may develop secondary to neutropenia which requires antibiotics or anti-fungal treatments.<sup>9</sup>

### Treatment

Since all neutropenia was grade 3–4, once it occurs, ICIs should be discontinued, and there is no report of ICIs rechallenge after granulocyte recovery. Corticosteroids and granulocyte colony-stimulating factors (G-CSF) were used in all patients, and granulocytes returned to normal after two weeks of treatment. Although steroids increase the risk of infections, G-CSF alone is not adequate. Other immunosuppressing agents, including mycophenolate mofetil, cyclosporin A and anti-thymocyte globulin (ATG) were administered to one patient with severe pancytopenia. In another patient, although ICIs were not reused after granulocyte recovery, neutropenia recurred at eight weeks after remission but recovered again with the same treatment.<sup>18–24</sup>

## Aplastic anemia (AA) and pure red cell aplastic anemia (PRCA)

The mechanism of bilineage or pancytopenia is similar to that of monolineage cytopenia. After ICI treatment, the expression of T cell receptor molecules, mainly CTLA-4 and PD-1 was downregulated, which contributes to the over-activation of immune responses. The inverted ratio of CD4/CD8 indicates inhibitory T cell sensitization. The mechanism shares some similarities with either AA or PRCA.

The most cases reported in a meta-analysis by Davis *et al.* demonstrated a total of 17 patients with AA +PRCA, with median ages of 59 and 65 years, respectively. The primary disease was mainly melanoma. Among these patients, 10 cases received anti-PD-1 antibody monotherapy. Similarly, many reasons account for pancytopenia, and AA itself is an exclusive diagnosis, so it is necessary to analyze other factors such as bacterial/viral infections and other drugs.<sup>8,9</sup>

### Clinical manifestations and differential diagnosis

AA/PRCA usually occurs approximately 10 weeks after ICI administration, which does not differ from other hematological adverse events (AEs). The neutropenia reaches grade 3–4, and anemia ranges from grade 2–4. There are reports of PRCA comorbid with AIHA. A severe decline of granulocytes leads to an increased risk of infections. Meanwhile, severe anemia is associated with the insufficient blood supply to organs such as the heart. Grade 4 thrombocytopenia may cause severe hemorrhage. In case of fever, bacterial and viral pathogens need to be examined, as well as parvovirus B19, especially when PRCA develops. It is recommended that bone marrow aspiration and biopsy should be performed to accurately evaluate cellularity and differentiate from other causes such as tumor infiltration. The immune-related AA has similar marrow changes compared with common AA, which manifests as distinct hypocellularity, usually without megakaryocytes observed. The proportion of erythroid hematopoietic cells in PRCA is less than 5%. High antinuclear antibody (ANA) titers may be found. Thus bone marrow examination is essential to rule out autoimmune-related pancytopenia,<sup>8,9,25–27</sup> in which bone marrow presents proliferative hematopoiesis.

### Treatment

Even if the risk of infection is high in AA/PRCA, all patients were treated with corticosteroids and cytokine supportive therapy, including G-CSF and thrombopoietin receptor agonists, accompanied by transfusion and antibiotics. Although ICIs were discontinued in all patients and were not reapplied, the efficacy of AA/PRCA was not as

optimistic as that of a monolineage cytopenia. Only three of the 17 patients in the study by Davis recovered completely, and one patient eventually died of infection due to neutropenia with fever. Patients with bilineage decline seemed to recover slightly faster.<sup>8,9,25–27</sup>

Despite the insufficiency of evidence, we recommend using corticosteroids usually prednisone or prednisolone 1 mg/kg. Other complementary methods include prophylactic antibiotics, antiviral and antifungal agents, with supportive G-CSF and blood transfusions. If resolution does not occur after two weeks, it is recommended that cyclosporine 3–5 mg/kg/day ± androgen should be added as soon as possible, or ATG if necessary. Meanwhile, the dose of steroids should be tapered.

## Hemophagocytic lymphohistiocytosis (HLH)

HLH is a rare, but critical syndrome in which inflammatory cytokines are massively activated, resulting in rapid multiple organ failure and high mortality. The clinical manifestations are nonspecific, which share many similarities with severe infections and tumor progression. Therefore, early recognition and treatment of HLH are pivotal to avoid progressive tissue damage.<sup>28</sup>

The largest report in the meta-analysis recruited 26 HLH cases, mostly patients with melanoma. CTLA-4 inhibitors were more common than PD1/PD-L1 mAbs (58% vs. 34%;  $P = 0.02$ ). HLH usually occurred at an early period after ICIs with a median 26 days. The associated mortality rate was 23%, the highest among all hematological adverse events.<sup>8</sup>

### Clinical manifestations and diagnosis/differential diagnosis

The diagnostic criteria of CIC related HLH refer to the 2004 standard, specifically including: (i) fever; (ii) splenomegaly; (iii) bilineage to trilineage peripheral cytopenia; (iv) hypertriglyceridemia ( $\geq 265$  mg/dL) and/or low fibrinogenemia ( $\leq 1.5$  g/L); (v) hemophagocytosis in bone marrow/spleen/lymph nodes; (vi) inhibited NK cell activity; (vii) serum ferritin  $\geq 500$   $\mu$ g/L and (viii) soluble CD25 (sIL-2 receptor)  $\geq 2400$  U/mL. The diagnosis of HLH is established if 5/8 or more criteria are met. Among them, ferritin exceeding 10 000  $\mu$ g/L has a sensitivity of 90% and a specificity of 96% for the diagnosis of HLH. The level of sCD25 helps to determine the severity of the disease.<sup>28</sup>

Approximately 19% of HLH patients were combined with EBV infection, indicating that the amplified immune response activates a potential viral infection. EBV or other infections can also trigger HLH, so bacterial culture or

relevant viral tests are required to troubleshoot other causes of HLH.

### Treatment

The treatment strategy of ICI-related HLH has no definitive guidelines to follow. The HLH-94 and 2004 protocols published by the International Society of Cellular Sciences are the accepted therapy which includes high-dose dexamethasone, etoposide or cyclosporine. Wang *et al.* from China combined liposomal doxorubicin, etoposide, and methylprednisolone as a promising salvage regimen in adult refractory HLH patients.<sup>29</sup> According to current reports, most patients only received high doses of prednisone or prednisolone 1–2 mg/kg, and a few were combined with mycophenolate mofetil or rituximab.<sup>7,30–32</sup>

It is recommended to use standard or high dose corticosteroids combined with etoposide based on the HLH international protocol. If front-line treatment fails, biological therapy (such as rituximab, infliximab, and etanercept), anti-interleukin-6 (tocilizumab) should be considered.

In conclusion, the immune-related hematological adverse events mainly manifest as monolineage or multilineage cytopenia, which could be life-threatening. Other even rarer AEs include acquired hemophilia A, eosinophilia, LGL, or HLH, etc. There is currently no standardized guideline for the diagnosis and treatment of hema-irAEs. Once hema-irAEs develop, it is recommended to perform blood and bone marrow examinations and to differentiate from infections and other drug-related AEs. High dose corticosteroids are the mainstay treatment, if necessary, combined with other immunosuppressive agents. Supportive treatments including prevention of infection, transfusion, etc are also very important for the resolution of irAEs. At present, there is not enough evidence for the rechallenge of ICIs.

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### Disclosure

The authors report that there is no conflict of interest to be disclosed.

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