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Review

Haematological immune-related adverse events with immune checkpoint inhibitors, how to manage?

J.M. Michot [a,b,*], J. Lazarovici [c], A. Tieu [b], S. Champiat [a], A.L. Voisin [d], M. Ebbo [e], B. Godeau [f], M. Michel [f], V. Ribrag [a,c], O. Lambotte [b,g,h,i]

[a] *Gustave Roussy, Université Paris-Saclay, Département des Innovations Thérapeutiques et Essais Précoces, Villejuif, F-94805, France*
[b] *Assistance Publique - Hôpitaux de Paris, Hôpital Bicêtre, Médecine Interne et Immunologie Clinique, Le Kremlin-Bicêtre, F-94275, France*
[c] *Gustave Roussy, Université Paris-Saclay, Département D'Hématologie, Villejuif, F-94805, France*
[d] *Gustave Roussy, Université Paris-Saclay, Unité de Pharmacovigilance, Villejuif, F-94805, France*
[e] *Assistance Publique - Hôpitaux de Marseille, Hôpital de La Timone, Médecine Interne, Marseille, F-13005, France*
[f] *Assistance Publique - Hôpitaux de Paris, Hôpital Henri Mondor, Médecine Interne, Centre de Référence des Cytopénies Auto-immunes de L'Adulte, Université Paris-Est Créteil, Créteil, F-94010, France*
[g] *INSERM U1184, Immunology of Viral Infections and Autoimmune Diseases, Le Kremlin-Bicêtre, F-94276, France*
[h] *Université Paris Sud, UMR 1184, Le Kremlin-Bicêtre, F-94276, France*
[i] *CEA, DSV/iMETI, IDMIT, Fontenay-aux-Roses, F-92265, France*

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Immune-related adverse event;

Abstract Immune checkpoint inhibitors (ICIs) are changing the treatments of many patients with cancer. These immunotherapies are generally better tolerated than chemotherapy, and their adverse events are immune-related mimicking autoimmune or inflammatory conditions. Although these immune-related adverse events mainly affect the skin, endocrine glands, digestive tract, joints, liver or lungs, all the organs can be theoretically affected, and the haematopoietic system is not spared. This review of the literature will focus on the haematological immune-related adverse events (Haem-irAEs). By reviewing the largest clinical trials of ICIs, we estimate the frequency of Haem-irAEs at 3.6% for all grades and 0.7% for grades III–IV. Frequency of Haem-irAEs of all grades was found to be higher with anti–programmed cell death 1 (4.1%) or anti–programmed cell death ligand 1 (4.7%) than with anti–cytotoxic T-lymphocyte–associated protein 4 (0.5%) ($p < 0.0001$). From the 63 cases with Haem-irAEs reported in the literature, the mean time to the onset was found to be 10 weeks after ICI initiation, and the large range for occurrence (1–84 weeks) and the regular incidence suggest that Haem-irAEs could occur at any time after ICI therapy. Among the 63 reported cases with

* *Corresponding author*: Gustave Roussy, Université Paris-Saclay, Département des Innovations Thérapeutiques and Essais Précoces, 114 rue Edouard Vaillant, Villejuif, F-94805, France. Fax: +33 142 116-444.
E-mail address: jean-marie.michot@gustaveroussy.fr (J.M. Michot).

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Immune checkpoint inhibitor;
Anti–programmed cell death 1;
Anti–programmed cell death ligand 1;
Anti–cytotoxic T-lymphocyte –associated protein 4

Haem-irAEs, the distribution was immune thrombocytopenia (n = 18, 29%), pancytopenia or immune aplastic anaemia (n = 12, 19%), neutropenia (n = 11, 17%), haemolytic anaemia (n = 10, 16%), cytokine release syndrome with haemophagocytic syndrome (n = 7, 11%) and other Haem-irAEs including bicytopenia or pure red cell aplasia (n = 5, 8%). Haem-irAEs are generally highly severe adverse reactions with a mortality rate of Haem-irAEs reported to be 14% (9 deaths among the 63 cases reported). The more severe and life-threatening Haem-irAEs were both cytokine release syndrome with haemophagocytic syndrome and pancytopenia or aplastic anaemia. Haem-irAEs induced by ICIs are potentially life-threatening. By discussing their pathophysiological aspects and clinical picture, we propose in this review clinical guidelines for management.

1. Introduction

Until the end of the 20th century, the four main weapons used against cancer were surgery, radiotherapy, chemotherapy and most recently targeted therapy. Immune checkpoint inhibitors (ICIs) are now becoming the fifth pillar of cancer treatment. These immunotherapies display clinically meaningful levels of effectiveness against many types of cancer, such as melanoma and lung, kidney and bladder cancer, Hodgkin lymphoma, primary B mediastinal lymphomas, Merkel cell carcinoma, and tumours with high-level of microsatellite instability [1].

The recent concept of immunoediting [2] was described as an immunological mechanism in the tumour microenvironment that favours the tumour growth, by exhaustion of T-cell signals mediated by cytotoxic T-lymphocyte–associated protein 4 (CTLA4), programmed cell death 1 (PD1) or programmed cell death ligand 1 (PD-L1). ICIs that target these checkpoints can reinvigorate cytotoxic T cells and thus restore the antitumoural immunity. By stimulating the immune system, these ICIs generate a new type of adverse events that mimic autoimmune conditions [1]. Both CTLA4 and PD1 have a physiological role in modulating the activation of T lymphocytes and thus preventing the occurrence of autoimmune disease under normal conditions [3]. By breaking this self-tolerance equilibrium, ICIs could induce adverse events that can mimic some well-known autoimmune or inflammatory diseases, such as Crohn disease, Hashimoto thyroiditis, psoriasis, vitiligo and sarcoidosis [1]. The most commonly affected tissues are the skin (vitiligo and skin rash), the gastrointestinal tract (Crohn-like or microscopic colitis), the endocrine system (thyroiditis, hypophysitis and pancreatitis), the liver (hepatitis), joints (tenosynovitis and polyarthritis), muscles (myositis or myocarditis), the lungs (interstitial pneumonias) and the nervous system or eyes (polyneuropathy, uveitis and so on) [1]. Finally, a growing body of evidence shows that immune-related adverse events (irAEs) can potentially reach all organs, and this translates into a broad spectrum of these immune-related clinical events (Fig. 1).

This review demonstrates that the haematopoietic system is not spared by these irAEs. Various types of immune cytopenia were reported such as immune thrombocytopenia (IT) [4], autoimmune haemolytic anaemia (AIHA) [5], neutropenia [6] or aplastic anaemia [7]. More recently, some cases of haemophagocytic syndrome (HS) [8,9] have also been described. Our group recently reported a series of 35 cases of haematological irAEs (Haem-irAEs) after anti-PD1 or anti–PD-L1 therapies [10]. Although the frequency of haematological toxicities was low (0.5%), the events recorded were often clinically serious and life-threatening; 27 (77%) of 35 patients with Haem-irAEs had a severity of grade IV or higher.

This review will estimate the frequency of Haem-irAEs from the safety data of the largest clinical trials. Second, we will propose to review all published cases in the literature to synthesise the knowledge on Haem-irAEs and to put forward some clinical management guidelines.

2. Pathophysiology

From a pharmacokinetic point of view, irAEs are dose dependent for anti-CTLA4, whereas for anti-PD1 or anti–PD-L1, irAEs are not expected to be dose dependent [11,12]. The difference in the dose-dependent toxicity profile between ICIs is considered related to the regulatory T cells (Treg)-depleting action [13] of anti-CTLA4, not exerted by anti-PD1 agents. From a clinical point of view, the profile of irAEs is different among ICI classes or PD-L1: anti-CTLA4 is expected to induce more frequent digestive and hypophysitis adverse events, whereas anti-PD1 or PD-L1 is associated with more frequent pneumonitis and arthralgia [1,14]. From a general point of view, the generation of irAEs could be associated with multiple biomarkers such as some autoreactive T cells [11], with elevated serum cytokines such as interleukin (IL)-17 [15], with the genetic

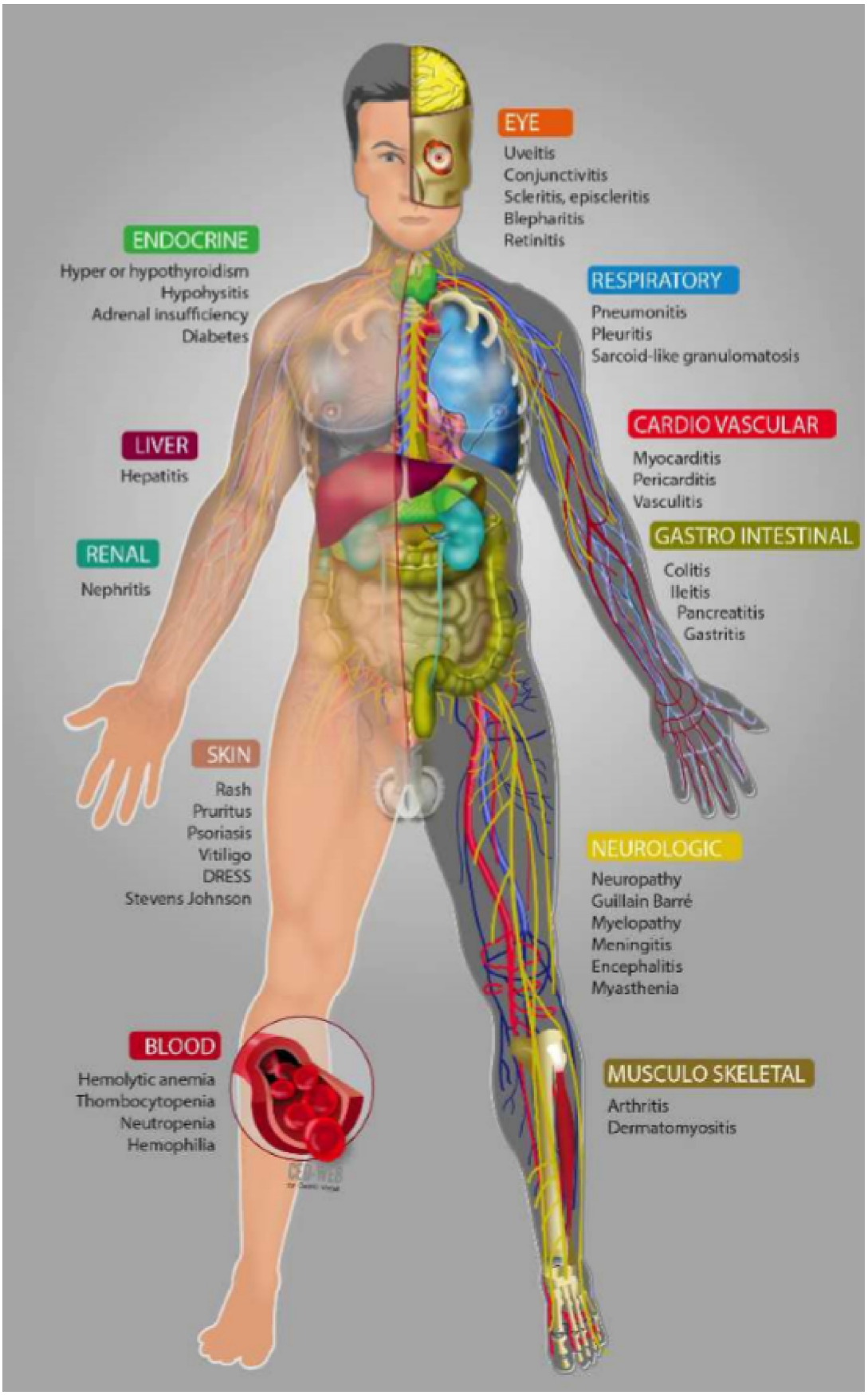

Fig. 1. The comprehensive clinical spectrum of immune-related adverse events induced by immune checkpoint inhibitors (courtesy of S. Champiat) [14]. aCTLA4: anti–cytotoxic T-lymphocyte–associated protein 4; aPD1: anti–programmed cell death 1; aPD-L1: anti–programmed cell death ligand 1.

background of individuals [16], or with the intestinal composition of the microbiome [17].

Little is known about the pathophysiology of Haem-irAEs. The recent report of four cases of nivolumab-induced aplastic anaemia in a single year suggests that PD1 might have a role in preventing aplastic anaemia [7]. The role of immune regulation by T cells was highlighted by the high expression levels of T-cell immunoglobulin mucin-3 and its ligand (galectin-9) in the blood of patients with acquired aplastic anaemia [18]. In the same way, PD1 was found strongly expressed on CD3+, CD4+ and CD8+ T cells in patients with aplastic anaemia [19]. All these data suggest that the PD1/PD-L1 axis should be crucial for preventing immune-mediated damage of the haematopoietic niche.

Some cases of immune haemolytic anaemia induced by anti-CTLA4 or anti-PD1 were recently described [5,20,21]. Importantly, ICIs were reported associated with the development of some red blood cell autoantibodies [22]. These cases of AIHA induced by ICIs were associated with a positive Coombs test [5,23], and other immune cytopenia such as neutropenia or thrombocytopenia was associated with anti-neutrophil or anti-platelet autoantibodies in serum of some patients [6,24]. These data imply that humoral immunity with autoantibodies can be implicated in Haem-irAE development.

Finally, our group recently reported that up to 9% of patients with Haem-irAEs treated for a solid tumour had a concomitant past medical history of chronic lymphocytic leukaemia (CLL), raising the question of a potential increased risk of haematological immunotoxicity in patients with an underlying mature lymphoid B clone [10].

3. Materials and methods

This review was based on comprehensive research on the PubMed database for English language publications (clinical trial reports, case series and cases reported up until July 2018). The ICI classes considered for this review were anti-CTLA4, anti-PD1 and anti–PD-L1 agents. The following keywords—medical subject headings—were selected: immune-related adverse event; immune thrombocytopenia; autoimmune hemolytic anemia; aplastic anemia; pancytopenia; pure-red cell aplasia; neutropenia; hemophagocytic syndrome; eosinophil count increase; immune-checkpoint inhibitor; anti-cytotoxic T-lymphocyte-associated protein 4, anti-programmed cell death 1; anti-programmed cell death ligand 1.

The frequency of Haem-irAEs was estimated on data extracted from large clinical trials that described haematologic adverse events in the safety analysis (anaemia, leucopenia, neutropenia or thrombocytopenia) and graded according to the common terminology criteria for adverse events (CTCAE) [25]. The selected studies had to provide enough data of safety on haematological adverse events and indicate the Haem-irAE relationship to the ICI treatment. Haematologic adverse events not related to ICIs were not included in this review. Of the 71 initially selected clinical trials, 19 provided enough detailed description of Haem-irAEs and were therefore reviewed for the estimation of frequency (Table 1). The frequency of Haem-irAEs was compared across anti-CTLA4, anti-PD1 and anti–PD-L1 agents by using a two-way analysis of variance test.

The aim of second part of the review was to describe Haem-irAEs type by type. For this purpose, we selected all types of Haem-irAEs reported in case series and case reports. The Haem-irAEs had to have been graded according to the CTCAE [25] with a grade of II or higher to be selected for this part of the review. Sixty-three cases of Haem-irAEs were addressed in this review (see references and detailed description in Supplementary data Table 1–Table 6). The time to onset from ICI initiation and the outcome of Haem-irAEs were pooled from all case reports and compared type by type, by using the Kruskal–Wallis test (a one-way analysis of variance test) or chi-square test, according to the numbers. All analyses were carried out with a risk of the first bilateral species of 5%. All analyses were performed as univariate analysis using SAS 9.4 and GraphPad Prism version 5.03 software.

4. Frequency and distribution

Based on the 19 selected studies of ICIs, the frequency of Haem-irAEs induced by ICIs was 3.6% for all grades and 0.7% for grades III–IV (Table 1). The frequency of Haem-irAEs of all grades were found to be higher with anti-PD1 (4.1%) or anti–PD-L1 (4.7%) than with anti-CTLA4 (0.5%) ($p < .0001$) (Fig. 2). From this analysis, it is highlighted that haematologic adverse events induced by ICIs are rare events and clearly much less frequent than the haematologic adverse events induced by cytotoxic chemotherapy [26].

By analysis of cases reported in the literature, a total of 63 cases reported Haem-irAEs of grade ≥II (Table 2). The median age of patients was 63 years. By the order of frequency, immune IT (29%), pancytopenia or aplastic anaemia (19%), neutropenia (17%), AIHA (16%), HS (11%) and other various types (8%) including bicytopenia and pure red cell aplasia (PRCA) were reported (Table 2 and Fig. 3A).

The mortality rate was found to be 14%, among all cases of Haem-irAEs (Table 2). By severity analysis and mortality of cases reported, HS were the most life-threatening condition reported (3 deaths on 7 cases reported), followed by pancytopenia or aplastic anaemia (4 deaths on 12 cases reported) (Table 2 and Fig. 3B). As shown in Fig. 4A, all types of haematologic irAEs were

Table 1
Incidence of ICI-induced, immune-related cytopenia (all grades and grades III–IV).

References	Phase	ICI	Organ	Dose	Patients (no. of patients who received ICIs)	Immune-related cytopenia, all grades,* % of patients (n)	Immune-related cytopenia, grades III–IV, % of patients (n)	Comments
Ascierto et al [12]	III	Ipi	Melanoma	3 or 10 mg/kg	726	0.6% (4)	0.7% (5)	Anaemia and pancytopenia
Robert et al [68]	III	Ipi (vs. Pembro)	Melanoma	3 mg/kg	256	0.4% (1)	0.4% (1)	Anaemia
Total for anti-CTLA4					**982**	**0.5% (5)**	**0.6% (6)**	
Ferris et al [69]	III	Nivo	Head and neck	3 mg/kg	236	5.1% (12)	1.3% (3)	Anaemia and neutropenia
Robert et al [70]	III	Nivo	Melanoma	3 mg/kg	206	4.4% (9)	0% (0)	Anaemia
Weber et al [71]	III	Nivo	Melanoma	3 mg/kg	272	3.7% (10)	0.7% (2)	Anaemia
Brahmer et al [72]	III	Nivo	Lung	3 mg/kg	135	2.3% (3)	0.8% (1)	Anaemia and neutropenia
Borghaei et al [26]	III	Nivo	Lung	3 mg/kg	292	2.4% (7)	0.3% (1)	Anaemia and neutropenia
Motzer et al [73]	III	Nivo	Renal cancer	3 mg/kg	406	7.9% (32)	1.7% (7)	Anaemia
Herbst et al [74]	III	Pembro	Lung	2 or 10 mg/kg	682	3.2% (22)	0.9% (6)	Anaemia and neutropenia
Reck et al [75]	III	Pembro	Lung	200 mg	154	5.8% (9)	1.9% (3)	Anaemia and leucopenia
Ribas et al [76]	II	Pembro	Melanoma	2 or 10 mg/kg	357	3.9% (14)	0.3% (1)	Anaemia and thrombocytopenia
Robert et al [77]	I–II	Pembro	Melanoma	2 or 10 mg/kg	173	3.5% (6)	0.6% (1)	Anaemia and thrombocytopenia
Garon et al [78]	I–II	Pembro	Lung	2 or 10 mg/kg	495	4.2% (21)	0% (0)	Anaemia
Hamid et al [79]	I–II	Pembro	Melanoma	2 or 10 mg/kg	135	8.2% (11)	0% (0)	Anaemia, neutropenia and thrombocytopenia
Bellmunt et al [80]	III	Pembro	Bladder	200 mg	266	3.8% (10)	1.5% (4)	Anaemia and neutropenia
Robert [68]	III	Pembro (vs. Ipi)	Melanoma	10 mg/kg	555	2.3% (13)	0.4% (2)	Anaemia and neutropenia
Total for anti-PD1					**4364**	**4.1% (179)**	**0.7% (31)**	
Fehrenbacher et al [81]	III	Atezo	Lung	1200 mg	144	6.3% (9)	0% (0)	Anaemia and neutropenia
Balar et al [82]	II	Atezo	Bladder	1200 mg	123	7.3% (9)	0.8% (1)	Anaemia and thrombocytopenia
Rosenberg et al [83]	II	Atezo	Bladder	1200 mg	310	2.9% (9)	1.0% (3)	Anaemia
Total for anti–PD-L1					**577**	**4.7% (27)**	**0.7% (4)**	
Total anti-PD1 + anti–PD-L1					**4941**	**4.1% (206)**	**0.7% (35)**	
Total ICI (anti-PD1 + anti–PD-L1 + anti-CTLA4)					**5923**	**3.6% (211)**	**0.7% (41%)**	

CTCAE: common terminology criteria for adverse events; CTLA4: cytotoxic T-lymphocyte–associated protein 4; PD1: programmed cell death 1; PD-L1: programmed cell death ligand 1; irAE: immune-related adverse event; ICI: immune checkpoint inhibitor; Ipi: ipilimumab; Nivo: nivolumab; Pembro: pembrolizumab; atezo: atezolizumab.
This table summarises the clinical trial studies that provide a full description of irAEs (graded according to the CTCAE [25]) and in which cytopenia was considered to be immune related.
* The grade of severity was assessed according to the CTCAE scale.

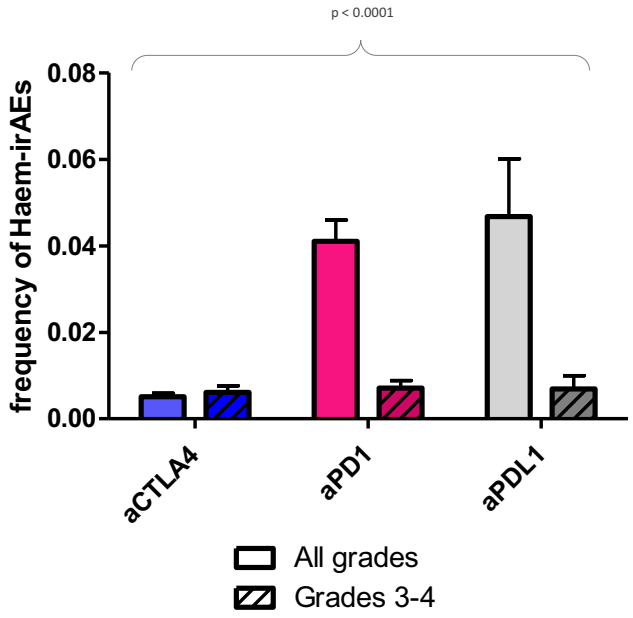

Fig. 2. Frequency of haematologic immune-related adverse events (Haem-irAEs) by the class of immune checkpoint inhibitors. The frequency of Haem-irAEs was compared across anti-CTLA4, anti-PD1 and anti–PD-L1 agents by using a two-way analysis of variance test. CTLA4: cytotoxic T-lymphocyte–associated protein 4; PD-L1: programmed cell death ligand 1; PD1: programmed cell death 1.

observed across all classes of ICIs (anti-PD1, anti–PD-L1 and anti-CTLA4) with a similar extent. Lower resolution rates were found with aplastic anaemia (25%) and HS (50%), compared with other immune Haem-irAEs ($p = 0.0459$) (Table 2 and Fig. 4B). The median time to Haem-irAE occurrence was 10 weeks, with a very wide range of the timing to occurrence (1–84 weeks). The curve of timing in occurrence of the Haem-irAE during ICI treatments shows a regular aspect suggesting that Haem-irAEs could occur at any time during ICI treatment (Fig. 5A). The PRCA or bicytopenia was found to occur lately, at a median (95% confidence interval) of 57 (10.4–97.2) weeks after ICI initiation ($p = 0.0477$) (Fig. 5B).

5. Type-by-type characteristics

5.1. Immune thrombocytopenia

Eighteen cases of ICI-induced IT were found [84–90] (detailed in Supplementary Table 1). The patients had taken anti-PD1 or anti-CTLA4 agents or a combination of both. The features of one case suggested that the antiplatelet autoimmunity generated by ICIs is cross-reactive between anti-CTLA4 and anti-PD1 agents [4]. The bone marrow aspirate—aspiration when performed—was suggestive of a peripheral mechanism of platelet destruction [27]. Fourteen patients received steroids, 10 of 14 (71%) achieved a good response with complete response ($n = 8$) or partial response ($n = 2$). The remaining four patients required additional treatment with rituximab or romiplostim with a good outcome [4]. At last follow-up, a full resolution rate of thrombocytopenia was achieved in 8 of 10 (80%) of patients. Of note, one patient was rechallenged without recurrence of IT.

5.2. Pancytopenia or aplastic anaemia

Twelve cases of ICI-induced pancytopenia or aplastic anaemia have been reported [91–97] (detailed in Supplementary Table 2). The clinical presentation was generally severe, cytopenia was profound and prolonged in almost all cases, and seven patients (58%) had clinical and/or histological features of life-threatening aplastic anaemia and were transfusion dependent. In some cases, the bone marrow biopsy showed activated CD8+ lymphocytes that was suggestive of immune-mediated aplastic anaemia [1]. Treatment was based on transfusions, haematopoietic growth factors, corticosteroids and immunosuppressive agents (cyclosporine or anti-lymphocyte serum [ALS]). Pancytopenia or aplastic anaemia appears as a severe adverse event as only 3 of 12 (25%) patients had a full resolution of the adverse event at the last follow-up, and four deaths related to the adverse event were recorded [7,28,29].

Table 2
Main characteristics of haematological irAEs, review of cases reported in the literature (detailed cases and references in the table in Supplemental Data).

Clinical types of haematological immune-related adverse events	Number of cases (%)	Median age in years (range)	Time to onset (in weeks)	Cases that resulted in deaths (%)	% of patients achieved a full resolution rate of the adverse event
ITP	18 (29%)	54 (34–78)	6 (1–20)	0	80
Pancytopenia or aplastic anaemia	12 (19%)	57 (42–78)	10 (2–72)	4/12 (33%)	25
Neutropenia	11 (17%)	63 (35–74)	10 (2–44)	0	82
AIHA	10 (16%)	70 (43–85)	6 (2–44)	1/10 (10%)	78
HS	7 (11%)	63 (42–81)	16 (1–68)	3/7 (43%)	50
PRCA/bicytopenia	5 (8%)	70 (32–73)	57 (18–84)	1/5 (25%)	80
Total cases	**63 (100%)**	**63 (32–85)**	**10 (1–84)**	**9/63 (14%)**	**79**

AIHA: autoimmune haemolytic anaemia; HS: haemophagocytic syndrome; ITP: immune thrombocytopenia; PRCA: pure red cell aplasia.

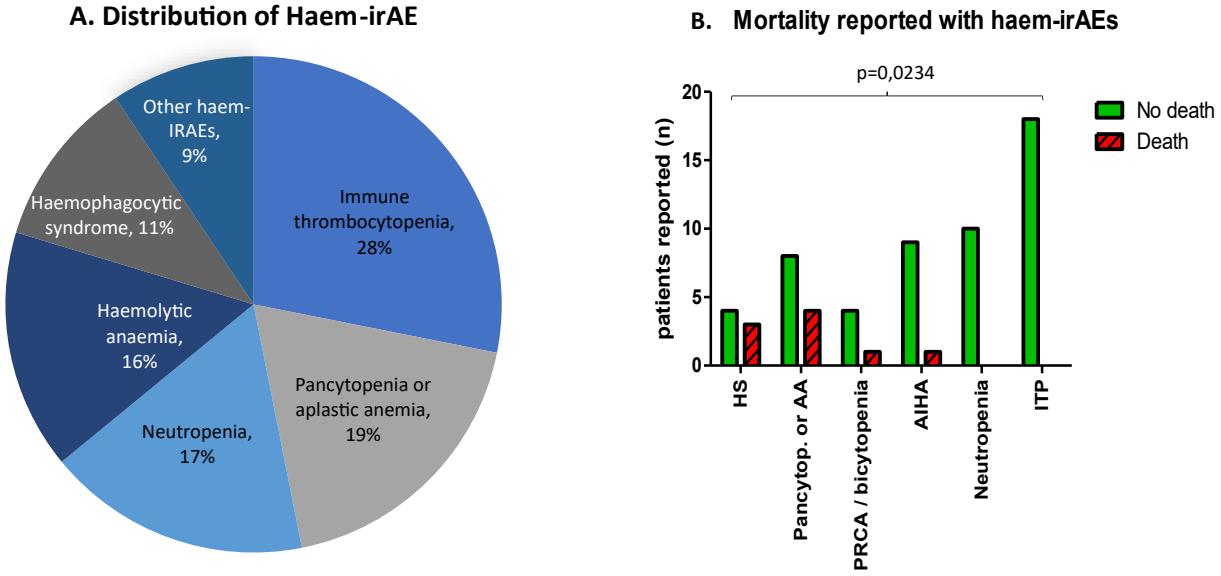

Fig. 3. (A) Distribution of grade II or higher haematologic immune-related adverse events (Haem-irAEs) reported in the literature. Data came from case series, case reports or supplementary material from clinical studies indexed in PubMed up until July 2018. (B) Mortality rates of Haem-irAEs among the 63 cases reported in the literature. The p value was calculated using the chi-square on an analysis contingency table. PRCA: pure red cell aplasia; AA: aplastic anaemia; AIHA: autoimmune haemolytic anaemia; ITP: immune thrombocytopenia; HS: haemophagocytic syndrome.

5.3. Neutropenia

Eleven cases of ICI-induced neutropenia were identified [98–100] (detailed in Supplementary Table 3). In all cases, neutropenia was profound and severe, with neutrophil counts close to 0/mm^3 in most of the cases [30–34]. Neutropenia was complicated with severe infection in 6 of 11 cases reported (55% of patients). The median duration of neutropenia under 500/mm^3 (grade IV) was 16.5 (range: 3–57) days. The work-up revealed large granular lymphocytes (LGLs) in one case tested [34] and serum antineutrophil antibodies in two of three cases tested [6,24]. Almost all the patients received granulocyte-colony stimulating factor for neutropenia. Other main treatments given for immune neutropenia were corticosteroids (n = 9), intravenous (i.v.) immunoglobulins (n = 5), cyclosporine (n = 3), rituximab (n = 2) or ALS (n = 2). At last follow-up, 9 of the 11

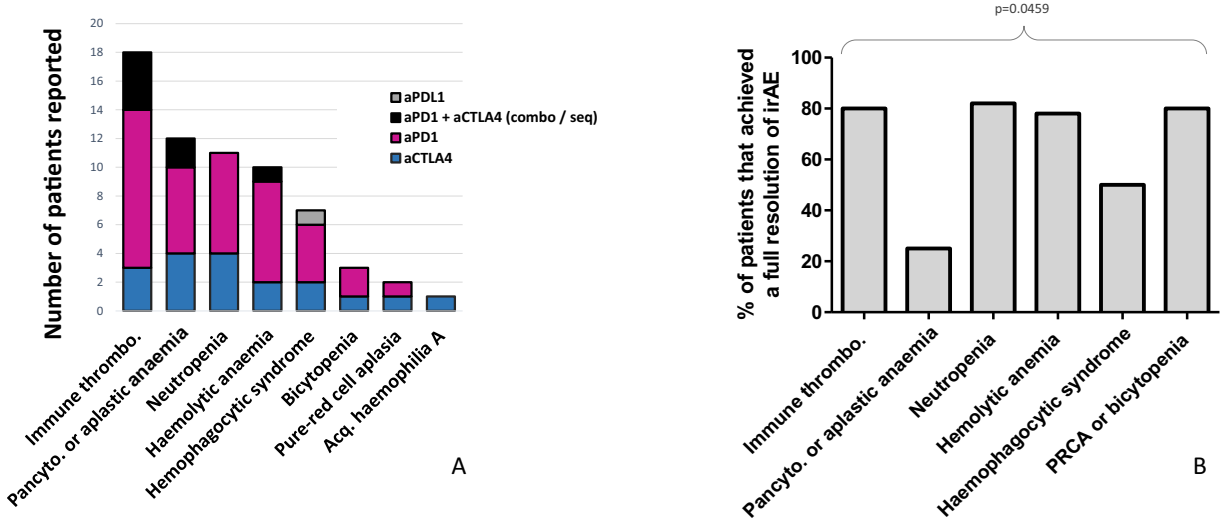

Fig. 4. (A) Distribution of grade II or higher haematologic immune-related adverse events (Haem-irAEs) reported in the literature across the class of immune checkpoint inhibitors. (B) Resolution rates of grade II or higher Haem-irAEs reported in the literature. Resolution rates were compared from a table of contingency using the chi-square test. Data came from case series, case reports or supplementary material from clinical studies indexed in PubMed up until July 2018. aCTLA4: anti–cytotoxic T-lymphocyte–associated protein 4; aPD1: anti–programmed cell death 1; aPD-L1: anti–programmed cell death ligand 1; irAE: immune-related adverse event; PRCA: pure red cell aplasia.

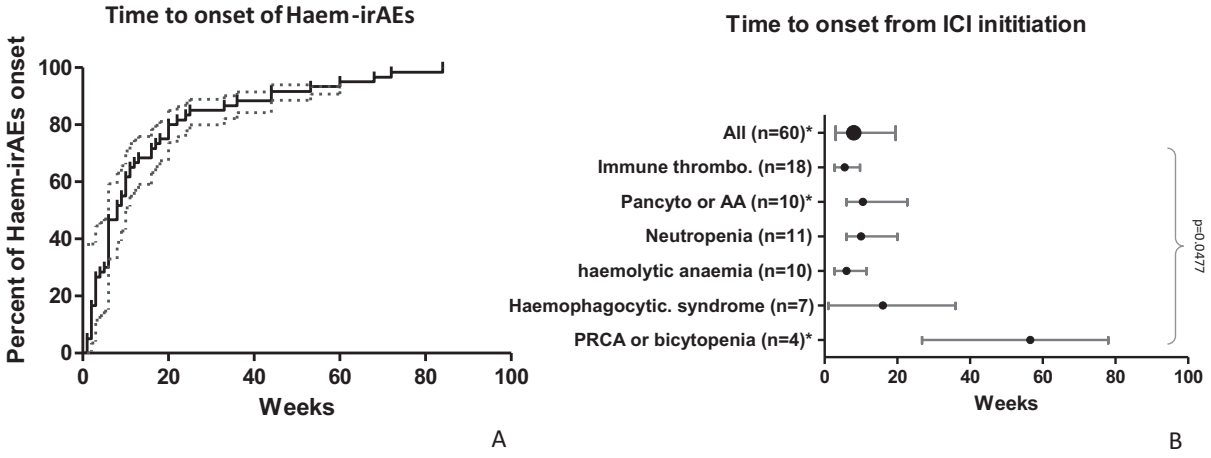

Fig. 5. Time to onset of haematologic irAEs (Haem-irAEs) from immune checkpoint initiation for all cases (A) and type by type (B). Data came from case series, case reports or supplementary material from clinical studies indexed in PubMed up until July 2018. The dashed lines in Fig. 5A indicate the error bars with 95% confidence interval. Each circle in Fig. 5B indicates the median, and error bars represent the interquartile range. The medians vary significantly ($p = 0.0477$) from one type of Haem-irAE to another, as assessed in a Kruskal–Wallis test (a one-way analysis of variance test). All patients: median (IQR) = 10.0 weeks (3.8–20.5). ITP group: median (IQR) = 5.5 weeks (4.2–10.8) weeks. Neutropenia group: median (IQR) = 10.0 weeks (4.9–22.8). Pancytopenia/AA group: median (IQR) = 10.5 weeks (2.6–32.0). AIHA group: median (IQR) = 6.0 weeks (1.0–19.2). HS group: median (IQR) = 16.0 weeks (1.0–43.0). PRCA/bicytopenia group: median (IQR) = 56.6 weeks (10.4–97.2). *The time to onset was not reported for three patients (data not available). AA: aplastic anaemia; AIHA: autoimmune haemolytic anaemia; HS: haemophagocytic syndrome; ICI: immune checkpoint inhibitor; Haem-irAE: haematological immune-related adverse event; IQR: interquartile range; ITP: immune thrombocytopenia; PRCA: pure red cell aplasia.

patients (82%) had achieved a full resolution of neutropenia. One patient was rechallenged without recurrence of neutropenia.

5.4. Autoimmune haemolytic anaemia

Haemolytic anaemia was reported in ten patients [101,102] (detailed in Supplementary Table 4) after treatment with anti-PD1 (n = 7), anti-CTLA4 (n = 2) or the combination of both (n = 1). Anaemia appeared around two months after the initiation of ICI treatment and was severe—below 8 g/dL (i.e. grade III or higher)—in all patients. The direct antiglobin test (DAT) was positive for IgG or C3 or both in all patients. Of note, two patients (20%) were found with a pre-existing history of B-cell chronic lymphocytic anaemia [35,36]. All 10 patients received corticosteroids, and two patients were additionally treated with rituximab [20] or cyclosporine [37]. The full resolution rate of haemolytic anaemia at last news was observed in 7 of 9 patients (78% of patients). After resolution, two patients were rechallenged, and one had a recurrence of haemolytic anaemia.

5.5. Cytokine release syndrome with HS

There were seven cases of cytokine release syndrome with HS reported after ICI treatment (detailed in Supplementary Table 5). Two cases of HS occurred after a combination of targeted therapies (BRAF and MEK inhibitors) given after anti-PD1 for metastatic melanoma [38]. Hence, this treatment sequence (targeted therapy, followed by ICI therapy) might induce more systemic inflammatory reactions [38], and overlap between cytokine release syndrome and HS is discussed in these cases. Most of the reported cases of HS were severe and life-threatening as it is usually observed with HS in general [1], and three of the seven reported patients died consecutively to HS induced by ICIs. Treatments given were corticosteroids, and 2 of the 7 (29%) patients had severe HS that required etoposide [8,9]. At last follow-up, a full resolution rate of HS was achieved in 3 of 6 (50%) patients with available data.

5.6. Eosinophil count increase

Some case series of eosinophil count increase related to ICI therapy were reported [39], providing that eosinophil count increase is generally mild to moderate (median increase count of 1000/mm^3) and asymptomatic in all cases [39]. Eosinophil count increase could be regarded as a clinically non-significant event [39]. The incidence of eosinophil count increase in patients treated with anti-PD1 or anti–PD-L1 was estimated to be 3% [39]. Interestingly, eosinophil count increase might be a predictive biomarker of a favourable antitumour response with anti-PD1 [40] or anti-CTLA4 agents [41] given for patients with melanoma. One anecdotal case of eosinophilia was reported as part of a drug reaction with eosinophilia and systemic symptoms related to ipilimumab [42].

5.7. Other Haem-irAEs

Other Haem-irAEs reported with ICIs are listed in Supplementary Table 5. Some of them are immune-mediated bicytopenia [103,104] (n = 3) and PRCA [105,106] (n = 2). Of note, the median onset of irAEs among patients with PRCA and bicytopenia could occur lately after ICI initiation (a median of 57 weeks, which ranged from 18 to 84 weeks).

6. Management in clinical practice

6.1. General management

The global management must apply from the moment the patient has been exposed with no time limit after exposure. Indeed, although most irAEs occur in the two first months of immunotherapy [13], some patients could experience irAEs later and sometimes even several months after treatment has been withdrawn [13]. When an irAE is suspected, the assessment of the severity according to the CTCAE [25], as well as relationship with the immunotherapy according to World Health Organisation Uppsala scale [43], has to be investigated with appropriate clinical and laboratory investigations [43].

Both European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) societies has issued guidelines on the management of ICI-induced adverse events [13,44]. Some institutional guidelines such as algorithms for the management of irAEs are also available, and we proposed in our institution the Gustave Roussy Oncology Handbook, a mobile phone application that can be downloaded free of charge from the App Store or Google Play [45]. Most patients with grade II or higher irAEs will be treated with steroids; consequently, a key point in the management of irAEs is also to prevent adverse events due to steroids such as opportunistic infections. Pneumocystis prophylaxis with trimethoprim and sulfamethoxazole (Bactrim®) may be offered to patients on prolonged corticosteroid use (>12 weeks) [14]. The role of prophylactic acyclovir with prolonged corticosteroid use (>12 weeks) remains unclear, and physicians should proceed according to institutional guidelines [14].

From a global point of view, ICI therapy should be continued with close monitoring for grade I toxicities, except for neurologic, haematologic and cardiac toxicities, for which toxicity even if grade I should lead to the discontinuation [13]. Holding ICI therapy is generally advised for most grade II toxicities, and the therapy is resumed when symptoms and/or laboratory values revert to grade I or lower. As irAEs are not dose dependent with most ICIs including the anti-PD1 or anti–PD-L1 class, dose adjustments are not recommended [13]. Oral corticosteroids with the initial dose of 0.4–1 mg/kg/day of prednisone or equivalent may be administered for some grade II irAEs [13]. For some more severe grade III or higher toxicities, high-dose i.v. corticosteroids are used, and generally, 5 mg/kg methylprednisolone boluses are used for 3–5 days. In case of grade III toxicity, immunotherapy must be discontinued until resolution or return to grade I. The risk of irAE recurrence being 50% in rechallenged patients, the discussion of rechallenge must be judged on a case-by-case approach depending on the expected benefit of immunotherapy and other therapeutic alternatives [46,47]. In general, grade IV toxicities warrant permanent discontinuation of ICI therapy, apart from some endocrinopathies that have been fully controlled by hormone replacement [13].

For haematological adverse events, the recommendations did not rely on large data and remained experience based. We highlight that caution should be exercised from these general guidelines based on the CTCAE or laboratory values [48], which does not always reflect the severity of the clinical situation. Some guidelines could lead to questionable management of some Haem-irAEs. For example, in the setting of immunological thrombocytopenia, the clinical severity score for haemorrhagic symptoms is more important than the single-laboratory platelet count [49], and the judgement of severity of bleeding risk could be different form one patient to another based on medical history and concomitant medication (e.g. anticoagulation therapy or aspirin use). Specific guidelines for Haem-irAEs are proposed in the following section.

6.2. Haematological assessment and investigations

For all Haem-irAEs, the first steps are to evaluate the change over time in blood count abnormalities, check the patient's previous blood counts and rule out any history of haematologic events. Most patients followed up in oncology departments have previously been exposed to cytotoxic chemotherapy and/or radiotherapy (i.e. treatments likely to induce myelodysplastic syndrome).

For the work-up of Haem-irAEs, the seven systematic following actions could be driven:

1. Complete haematological laboratory tests including determination of haemostasis (prothrombin time, activated partial thromboplastin time and fibrin level) to rule out any disseminated intravascular coagulation. In cases of thrombocytopenia, the physician must look for hepatic and splenic causes of platelet sequestration, frequently associated with thrombocytopenia. Other basic haematological laboratory tests are blood smear, reticulocyte count, biochemical parameters for haemolysis (lactate dehydrogenase, bilirubin and haptoglobin) and the direct antiglobulin test (DAT); all are essential for determining underlying mechanism of anaemia.
2. Consider bone marrow analysis as this is generally mandatory in cases of non-regenerative cytopenias (bicytopenia and pancytopenia), by bone marrow aspiration or

bone marrow biopsy. Bone marrow analysis allows determining if cytopenia is of central or peripheral origin. Haematologists should advice the cause of cytopenia with both the bone marrow smear and blood smear. For pancytopenia investigation, bone marrow biopsy is the key examination for determining whether the cause of cytopenia is central or peripheral and making a formal bone marrow tissue diagnosis of aplastic anaemia.

3. Check whether another drug is responsible as it can potentially be involved in cytopenia, this work has to be carried out jointly with the pharmacovigilance team.
4. Rule out infection and especially a viral cause by running systematic serologic assays for HIV and hepatitis C. Depending on the context (fever, mononucleosis syndrome and so on), screening for other primary viral infections or viral reactivations such as herpes group virus (e.g. herpes simplex virus [HSV] 1 and HSV2, cytomegalovirus [CMV] or varicella zoster virus), Epstein–Barr virus (EBV) or parvovirus B19 with polymerase chain reaction (PCR) assays and serologic tests is necessary. Some parasitological tests in blood and bone marrow should be performed depending on the region, for example, PCR assay for leishmania for endemic regions.
5. Check for a potential underlying haematological malignancy. A simple blood smear examination by an advised cytologist allows ruling out not only haematologic proliferation (such as chronic B-cell leukaemia) but also thrombotic microangiopathy (a high schistocyte count) or bone marrow infiltration by solid tumour metastasis (indirect signs could be seen such as myelocytosis). In cases of AIHA, IT or B-cell CLL, immunophenotyping of circulating lymphocytes should be performed, and in cases of immune neutropenia, search for T-cell LGLs.
6. Search for a potential underlying autoimmune disease, such as systemic rheumatoid arthritis or lupus, autoimmune endocrinopathy, skin autoimmunity and so on. Autoimmune nuclear antibody testing including that of anti-DNA antibodies is a rapid and sensitive test to screen some autoimmune diseases. In cases of neutropenia or haemolytic anaemia, screening for autoantibodies against neutrophils or red blood cells (using the DAT and antineutrophil/antinuclear antibody assays) could be useful. Screening for antiphospholipid syndrome potentially associated with IT should be useful.
7. In cases of high fever (higher than 39°C–40°C) with cytopenias, the diagnosis of cytokine release syndrome with HS must be promptly considered. Complete laboratory investigations including ferritin, triglycerides and fibrinogen could lead to the calculation of a probability score to help in the diagnosis of HS. The treatment for cytokine release syndrome with HS should be given with any delay and is detailed in the following section, and given the potential severity of this condition, the patient should be managed with an intensive care team.

6.3. Type-by-type guidance for Haem-irAEs

The key points of the characteristics and management of haematological adverse events are summarised in Table 3.

6.3.1. Immune thrombocytopenia

First assessment is based on the clinical bleeding symptoms in skin (petechiae or haematoma), mucosal oral (bleb bleeding in the mouth) or organs (digestive tract and so on). The bleeding symptoms quantified using a simple bleeding score is the most relevant for evaluation of the severity of IT. (The bleeding score is shown in Table 4 [49].) In cases with a high bleeding score (>8, according to Khellaf *et al.* [49]), immediate treatment with polyvalent i.v. immunoglobulins (IVIGs) should be given, in combination with corticosteroids, as summarised in Fig. 6. Corticosteroids are given intravenously in severe cases using methylprednisolone or dexamethasone, but more often, prednisone is used orally at a dose of 1 mg/kg/day for three consecutive weeks. After three weeks, the corticoids can then be stopped or rapidly withdrawn as there is no need to progressively taper them in the context of IT. Platelet transfusions are generally not effective and are only recommended if the bleeding is life-threatening or has a major functional impact on an organ such as the eye or neurologic system. If a patient does not respond to steroids or has developed chronic IT, treatment with a thrombopoietin receptor agonist [50] or rituximab [51] may be offered on a case-by-case approach, depending on the risk/benefit ratio. Finally, the management of anti-PD1–induced IT should follow that of classical primary IT, as reported in recent consensus guidelines [52]. We recently found that IT is frequently resolving with steroids or IVIG or eventually rituximab [10], and if patients could benefit from anti-PD1 therapy, rechallenge could be reasonably discussed in some patients.

6.3.2. Aplastic anaemia or pancytopenia

Aplastic anaemia should be suspected in cases of pancytopenia occurring after the administration of ICIs. The etiological work-up [53] is based on a bone marrow biopsy, karyotyping and screening for a paroxysmal nocturnal haemoglobinuria clone (using flow cytometry immunophenotyping). The severity of the bone marrow failure is assessed with the index used by Camitta et al [54]. Any severe features (such as profound cytopenia requiring transfusions) will require appropriate, emergency management by a specialist haematologist [53]. Given the severity of the cases induced by ipilimumab and by anti-PD1 agents [7], ICI therapy should be generally managed by permanent discontinuation.

Treatment of immune-related aplastic anaemia should be based on corticosteroids, granulocyte-colony stimulating factor (GCSF) and eventually immunosuppressive therapy such as cyclosporine [53]. In severe cases, other therapies such as those with the thrombopoietin receptor agonist [55] or ALS should be regarded, on case-by-case approach.

Table 3
Assessment and management of haematologic immune-related adverse events induced by immune checkpoint inhibitors.

Condition	Circumstances of occurrence	Clues from the patient outcome	Haematologic and serologic findings	General management
Immune thrombocytopenia	Fortuitous or bleeding symptoms	Bleeding symptoms should be carefully screened by clinical and laboratory examination (bleeding score [49]). Resolution most often after treatment.	Peripheral thrombocytopenia on bone marrow aspiration. Antiplatelet antibodies in serum possibly positive.	Full dose of corticosteroids (1 mg/kg/day) for three consecutive weeks. No tapering is required. In case of significant bleeding, (bleeding score >8) [49] administer IVIG immediately in addition of steroids. In case of insufficient response to corticosteroids, may propose rituximab or agonists of thrombopoietin. Resolution most often, making resumption by immunotherapy an option.
Pancytopenia or aplastic anaemia	Fatigue due to anaemia and bacterial infections due to neutropenia	Cytopenias are often prolonged and requires significant transfusion support. Often bone marrow failure, and a low-resolution rate.	Bone marrow biopsy must be performed to diagnose aplastic anaemia. Bone marrow richness is generally poor or desert.	Encourage hospitalisation for the management of neutropenia and to control the risk of infection. Give corticosteroids and supportive care with GCSF. In case of insufficient response to corticoids, consider ciclosporin or thrombopoietin agonists. Antilymphocyte serum to be considered in patients with no comorbidity. Low-resolution rate and severe side-effect, discouraging the resumption of immunotherapy.
Neutropenia	Often asymptomatic at the beginning, otherwise infectious. Generally deep neutropenia close to 0/mm^3.	Life-threatening condition by the bacterial infection, risk at the nadir of neutropenia. Neutropenia under 500/mm^3 usually lasts two weeks.	Peripheral neutropenia on bone marrow aspiration. Antineutrophil antibodies eventually positive. Screening for underlying large granular lymphocytes.	Encourage hospitalisation for the management of neutropenia and control the risk of infection. Give GCSF daily until leucocyte recovery and ad hoc anti-infectious treatments. Do not give corticosteroids systematically as they could increase the risk of infection. High resolution rate but severe adverse events, to be carefully discussed before resumption of immunotherapy.
Haemolytic anaemia	Fatigue and anaemia due to haemolysis (decreased haptoglobin, increased LDH, peripheral anaemia with increase in reticulocyte count).	Often sudden onset of deep regenerative anaemia. Resolution most often after treatment.	Bone marrow analysis is not mandatory for peripheral haemolytic anaemia diagnosis. Positive direct antiglobulin test (both warm or cold temperature of agglutination is possible). Underlying chronic B lymphocytic leukaemia to be diagnosed by phenotyping blood.	Corticosteroids at a dose ≥1.5 mg/kg/day for 15 consecutive days, followed by progressive tapered dosing. Red blood cell transfusion support if needed, carefully given and after steroid start. In case of incomplete response to steroids on day 15, may offer rituximab. High resolution rate but severe adverse event, to be carefully discussed before resumption of immunotherapy.
Cytokine release syndrome with haemophagocytic syndrome	Highly febrile patients (higher than 39°C–40 °C) with cytopenias.	High fever and impaired general condition. Haemophagocytic syndrome overlap with cytokine release syndrome. Generally important which is a severe, life-threatening condition.	The H-score is a simple test to assess the probability of haemophagocytic syndrome [66]. Elevation of levels of ferritin, triglycerides and soluble CD25 receptor. In bone marrow aspiration, the classic picture of haemophagocytosis could be absent and is not required for the formal diagnosis of HS.	Patients to be hospitalised with intensive care consideration. Intravenous high-dose corticosteroids (3–5 mg/kg/day) with anti–IL-6 (tocilizumab or siltuximab) should be promptly given. In case of insufficient response, give consider etoposide 150 mg/kg intravenously as a single dose. This adverse event is generally severe and could discourage the resumption of immunotherapy.

Pure red cell aplasia or bicytopenia	Fatigue due to anaemia. Bicytopenia or non-regenerative anaemia (low reticulocyte count).	May occur a long time after the start of immunotherapy. Resolution of irAEs most often after steroid treatment.	Bicytopenia is of central origin on the bone marrow. The direct antiglobulin test may be positive. Check systematically for parvovirus B19 virus.	Corticosteroids at doses more than 1.5 mg/kg/day for 15 days, followed by the progressive tapered dose. Red blood cell transfusion support if needed. If an incomplete response on day 15, may offer rituximab or ciclosporin. May offer IVIG in case of parvovirus B19 infection. High resolution rate but severe adverse event, to be discussed carefully before the resumption of immunotherapy.
Eosinophil count increase	Fortuitous as patients are asymptomatic	Eosinophil count increase is a non-clinically significant event.	No specific examination is required for asymptomatic patients.	No specific treatment is required. The ICI treatment should be continued without interruption in asymptomatic patients.

ICI: immune checkpoint inhibitor; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; irAE: immune-related adverse event.

6.3.3. Neutropenia

Occurrence of grade II or higher neutropenia should push the physician to examine the blood smear and bone marrow aspirate, to rule out any underlying blood disease or drug-related myelodysplastic syndrome [56]. The patient's recent medical history should be screened for any other medications known to potentially induce neutropenia (cotrimoxazole, clozapine, propylthiouracil and other thionamides, penicillin, piperacillin-tazobactam, rituximab, flecainide, metformin, colchicine and so on) [56,57]. Neutropenia could be associated with abnormal T or natural killer (NK) lymphocytes called LGLs, which should be screened using blood and bone marrow smears and if the LGL count is $>0.5 \times 10^9$/L by T and NK lymphocyte immunophenotyping.

Antinuclear or antigranular antibody assays may be of value in characterising the autoimmune nature of the neutropenia [58]. Main complications of neutropenia are infection, and the estimation of the risk of infections is

Table 4
The bleeding score of Khellaf and al. for evaluation of severity of immune thrombocytopenia and indication for intravenous immunoglobulin (IVIG). Courtesy of M Khellaf (M Khellaf, Haematologica 2005 [49]).

Age	
Age more than 65 years	2
Age more than 75 years	5
Cutaneous bleeding[a]	
Localised petechial purpura (legs)	1
Localised ecchymotic purpura	2
Two locations of petechial purpura (e.g. legs + chest)	2
Generalised petechial purpura	3
Generalised ecchymotic purpura	4
Mucosal bleeding	
Unilateral epistaxis	2
Bilateral epistaxis	3
Haemorrhagic oral bullae, spontaneous gingival bleeding or both	5
Gastrointestinal bleeding[a]	
Gastrointestinal haemorrhage without anaemia	4
Gastrointestinal haemorrhage with acute anaemia (>2 g Hb decrease in 24 h) and/or shock	15
Urinary bleeding[a]	
Macroscopic haematuria without anaemia	4
Macroscopic haematuria with acute anaemia	10
Genitourinary tract bleeding[a]	
Major menorrhagia/metrorrhagia without anaemia	4
Major menorrhagia/metrorrhagia with acute anaemia	10
Central nervous system bleeding	
Central nervous system bleeding and/or life-threatening haemorrhage	15

Khellaf and al. [49] proposed to give IVIG for patients with platelet counts under 20 × 109/L and a bleeding score higher than 8 or contraindications to steroids (see the therapeutic strategy in Fig. 6).

[a] For these items, only the highest value was taken into account.

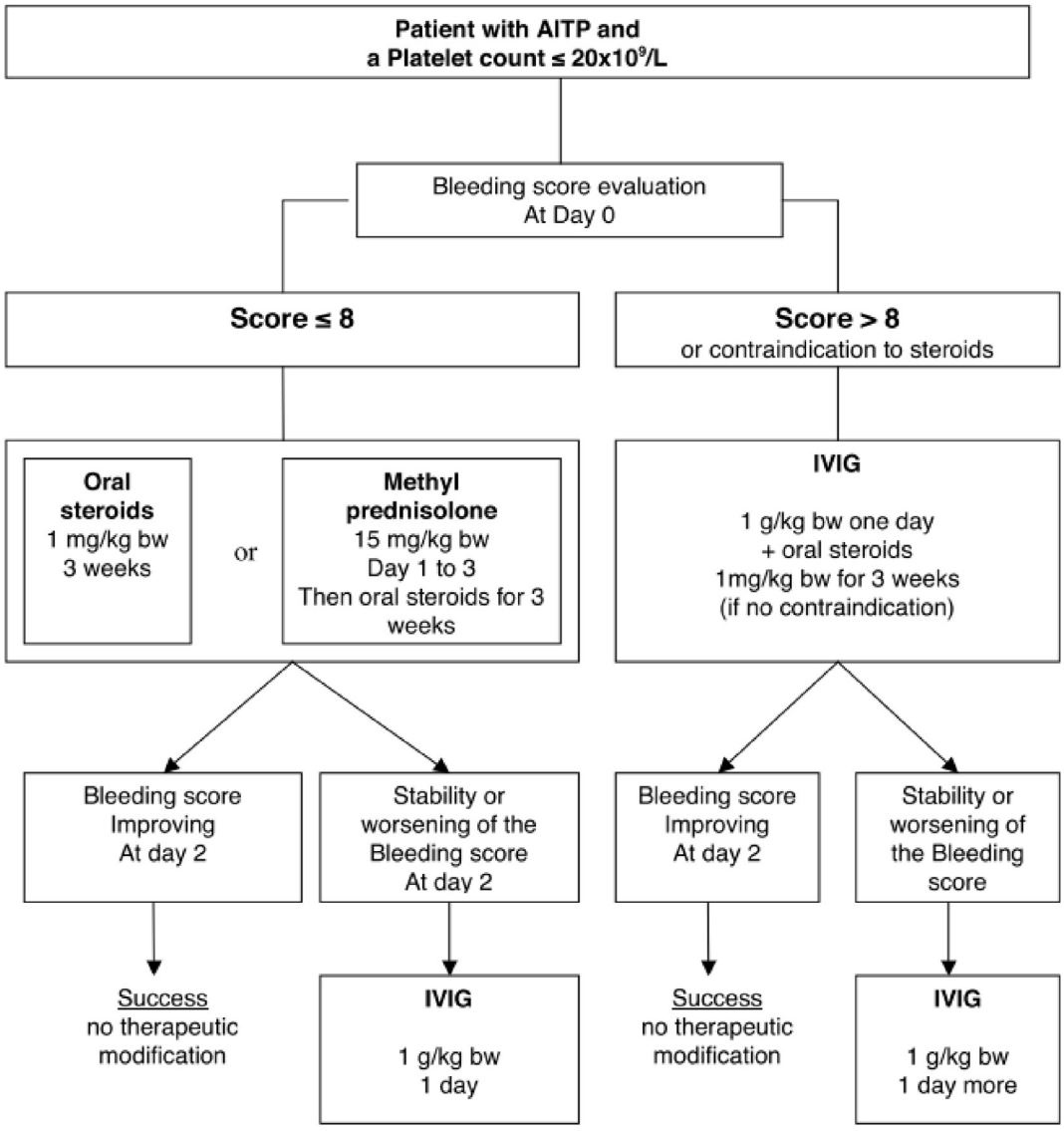

Fig. 6. Therapeutic strategy for the management of patients with autoimmune thrombocytopenia (AITP) with a platelet count of $\leq 20 \times 10^9$/L. Courtesy of M Khellaf (M Khellaf, Haematologica 2005 [49]).

based on the clinical history, depth and duration of neutropenia. High-risk patients should be encouraged for hospitalisation to manage neutropenia and treat potential infections immediately. In cases of febrile neutropenia, antibiotics (usually a wide spectrum antibiotic) should be immediately administered. GCSF should be administered daily until leucocyte count recovery. Without any firm evidence of efficacy, corticosteroids should not be given systematically as they could accentuate the risk of infection [56]. In cases of persistent, GCSF-refractory neutropenia, cyclosporine can be considered after discussion with an expert haematologist [59,60].

6.3.4. Autoimmune haemolytic anaemia

We and others reported that both types of warm and cold AIHA were reported with ICIs [10,20,35,36]. Distinguishing warm and cold types of AIHA is important as treatments are different, and in cold antibody cases, steroids are deemed with poor efficacy [61]. Autoimmune anaemia is characterised by a positive serum DAT by anti-IgG/IgM or anti-IgG/IgA and/or an antiC3d, and the characterisation of the thermal optimum reaction distinguishes between cold or warm AIHA. In all cases, symptomatic treatments for AIHA such as transfusion of preheated red blood cells for cold antibody cases and folic acid supplementation should be given (orally 5 mg/daily).

The cold antibody (usually an IgM with a C3-type positive DAT) can be due to a viral (e.g. CMV or EBV) or bacterial (e.g. *Mycoplasma pneumoniae*) infections. Cold antibody could also be associated with a low-grade B-cell lymphoproliferation with monoclonal gammopathy IgM kappa, referred to as the cold agglutinin

disease. In haemolytic anaemia induced by cold antibodies, corticosteroids are notoriously ineffective. Treatment is based on rituximab, eventually combined with chemotherapy with an alkylating agent [61].

Of note, before using rituximab, an active viral infection, especially hepatitis B, should be ruled out or treated. The warm antibody is generally associated with an autoimmune condition (e.g. lupus erythematosus) or an underlying lymphoid malignancy (e.g. B-cell chronic lymphoid leukaemia or non-Hodgkin B-cell marginal zone lymphoma). Screening for circulating monoclonal B-cell lymphocytes by blood immunophenotyping is recommended. The treatment of warm antibody AIHA is based on corticosteroids, usually oral prednisone, given at a starting dose of 1.5 mg/kg/day [61] that must be maintained for at least 2 weeks and until achievement of the haemoglobin level >12 g/dL. Thereafter, prednisone is to be decreased progressively and slowly tapered, by 20 mg every week, until a dose of 20 mg daily is reached, followed by a slower taper over 4–8 weeks. Haemoglobin levels should be monitored on a weekly basis until the tapering process is complete. Although one might be tempted to discontinue corticosteroids more rapidly, patients with AIHA should be treated for at least three months with low doses of prednisone (≤10 mg/day) [61]. In any cases, folic acid supplementation should be given. For patients who do not achieve a complete response at day 15 of corticosteroid therapy or in relapsed cases, second-line therapy with rituximab may be added as this treatment is effective in up to 80% of patients [62,63].

6.3.5. Cytokine release syndrome with HS

Cytokine release syndrome and HS are overlapping conditions, and HS should be regarded as a complication of a cytokine release syndrome [64]. In cases of high fever (more than 39°C–40°C) with cytopenias, the diagnosis of cytokine release syndrome with HS must be promptly considered. Febrile cytopenia constitutes a medical emergency; hospitalisation is generally more appropriate to manage patients, and patients should be managed with an intensive care team. In a context of fever cytopenia, it may be instructive to screen for HS using rapid laboratory tests such as determination of serum ferritin and triglyceride levels, both generally elevated in HS. The soluble CD25 receptor is often found elevated; however, this test is not available everywhere [65]. A bone marrow aspirate should be screened for the cause of cytopenia and haemophagocytosis; however, the classical haemophagocytic picture could be absent and is not mandatory for retaining this diagnosis formally. A simple and rapid clinical and laboratory score (H-Score, detailed in Table 5) is useful for assess the probability of HS diagnosis [66].

In the absence of an infectious cause, the treatment of HS is based on high-dose (2–5 mg per kg) corticosteroids to be given intravenously and to promptly block the hyperinflammatory process. As there is a continuum between immunological fever, cytokine release syndrome and HS induced by anti-PD1 or PD-L1 [8,64], this continuum should motivate use of anti–IL-6 therapy (such as tocilizumab or siltuximab) in severe cases in patients who did not satisfactorily respond to steroids [64]. In cases of insufficient response to these therapies, i.v. etoposide generally at a dose of 150 mg/kg as a single dose should be given to control HS [67].

Table 5
Parameter and number of points used to calculate the H-Score.

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression[a]	0 pt (no) 18 pts (yes)
Temperature (°C)	0 pt (<38.4) 33 pts (38.4–39.4) 49 pts (>39.4)
Organomegaly	0 pt (no) 23 pts (hepatomegaly or splenomegaly) 38 pts (hepatomegaly and splenomegaly)
No. of cytopenias[b]	0 pt (1 lineage) 24 pts (2 lineages) 34 pts (3 lineages)
Ferritin (ng/ml)	0 pt (<2000) 35 pts (2000–6000) 50 pts (>6000)
Triglyceride (mmoles/liter)	0 pt (<1.5) 44 pts (1.5–4) 64 pts (>4)
Fibrinogen (gm/liter)	0 pt (>2.5) 30 pts (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 pt (<30) 19 pts (≥30)
Haemophagocytosis features on the bone marrow aspirate	0 pt (no) 35 pts (yes)

pt(s): point(s)
The H-Score is a diagnostic score for reactive haemophagocytic syndrome. The probability of having haemophagocytic syndrome ranged from <1% with an H-Score of <90 to >99% with an H-Score of >250. The H-Score can be used to estimate an individual's risk of having reactive haemophagocytic syndrome. This scoring system is freely available online at http://saintantoine.aphp.fr/score/. Courtesy of L Fardet. Fardet L, Arthritis and Rheumatology, 2014 [66].
[a] Being human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e. glucocorticoids, cyclosporine, azathioprine).
[b] Defined as a hemoglobin level of ≤ 9.2 gm/dl and/or a leukocyte count of ≤ 5,000/mm3 and/or a platelet count of ≤ 110,000/mm3.

6.3.6. Eosinophil count increase

This laboratory abnormality is usually considered with no clinical translation and is therefore benign [39,41]. Asymptomatic eosinophilia could be regarded as a non-clinically significant event. Hence, in asymptomatic patients and in the absence of other adverse events, any specific treatment is required, and ICIs can be

continued. In symptomatic patients, the examinations will be driven by the symptoms, thinking that eosinophilia may primarily reflect an immunoallergic cause (e.g. asthma) or a cause of parasitic infection (e.g. parasitological examination of the stool to be performed if appropriate).

7. Conclusion

The haematopoietic system could be affected by irAEs, with a frequency of 3.6% for all grades and 0.7% for grades III–IV. These haematologic adverse events are various types of immune cytopenias such as immune thrombocytopenia, pancytopenia or aplastic anaemia, neutropenia, haemolytic anaemia, PRCA and cytokine release syndrome with HS. Haematological adverse events were found to be a potentially severe and life-threatening autoimmune complication of anti-PD1 or PD-L1. Aplastic anaemia and cytokine release syndrome with HS were found to be the most severe and life-threatening complications. Future research should investigate haematological adverse events to find some ways to early detect and better manage them in clinical practice.

Author contributions

J.M.M., O.L. and A.T. designed the research. A.T., A.L.V., O.L. and J.M.M. performed the research and data collection. J.M.M., O.L., M.E., S.C. and A.L.V. analysed the data. A.T., J.M.M., O.L., V.R., M.M. and B.G. wrote and edited the article.

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Appendix A. Supplementary data

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