CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4

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In this chapter, we describe observed infectious complications associated with the use of monoclonal antibodies (MoAb) against surface antigens CD22, CD30, CD33, CD38, CD40, SLAMF-7 (CD319), and CCR-4 predominantly in patients with hematologic malignancies. A summary of the infectious complications documented in randomized studies is presented in Table 6.1. Because of the shared presence of these antigens on various malignant cells and healthy immune system cells, infections associated with immunosuppression are often observed with these agents, and proper monitoring and prophylaxis are important aspects for their use in clinical practice. The overall risk of specific infections and proposed management is summarized in Table 6.2. We limit this chapter to unconjugated (or naked) and conjugated MoAb to toxins (antibody drug conjugates, ADC) as previously reviewed by the author [1]. ADC exploit the specific binding properties of MoAb for selective delivery of cytotoxic agents to tumor cells. There are three necessary components of ADC: the antibody, cytotoxic agent, and covalent linker [2]. This chapter does not cover bispecific MoAb (so called BiTEs) or chimeric antigen MoAb (CARTs), as they are analyzed in other chapters. The mechanisms of action of naked and conjugated targeted monoclonal antibodies revised in this chapter are schematically illustrated in Fig. 6.1.

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Table 6.1 Summary of infectious complications in patients treated with agents targeting CD22, CD30, CD33, CD38, CD40, SLAMF7, and CCR4 (studies with control group)

Drug	Type of study [ref]	Treatment arms	No. of subjects	Rate of infections (drug vs. comparator)
Epratuzumab	Two phase 3 RCTs for SLE [6]	Epratuzumab (600 mg/m^2 weekly or 1200 mg/m^2 every 2 weeks) plus standard therapy vs. placebo plus standard therapy	1048 vs. 526	Overall infection: 52–61% vs. 60%; URTI: 12–15%vs. 11–14%; UTI: 10–14% vs. 11–18%; VZV: 1–4% vs. 2–3%
Inotuzumab ozogamicin	Phase 3 RCT for relapsed or refractory ALL [7]	Inotuzumab-ozogamicin vs. standard therapy	109 vs. 109	Febrile neutropenia (grade 3–4): 11% vs. 18%; pneumonia: 4% vs. 1%; sepsis: 2% vs. 5%; septic shock: 1% vs. 1%
Inotuzumab ozogamicin	Phase 2 study in newly diagnosed ALL in patients >60 years [9]	Standard therapy + inotuzumab ozogamicin vs. standard therapy	58 vs. 77	2 sepsis vs. 10 sepsis
Inotuzumab ozogamicin	Phase 3 RCT in relapsed or refractory ALL [8]	Inotuzumab-ozogamicin vs. standard therapy	164 vs. 143	Febrile neutropenia (all grades): 11.6% vs. 18.9%; sepsis 2.4% vs. 7.0%
Brentuximab vedotin	Phase 3 RCT for consolidation therapy after autologous HSCT in Hodgkin lymphoma [18, 66]	Brentuximab vs. placebo	167 vs. 160	Neutropenia:35% vs. 12%; URTI 26% vs. 23%; severe infection: 9% vs. 4%; VZV/HSV infection: 19 vs. 5 patients
Brentuximab vedotin	Phase 3 RCT in advanced stage Hodgkin lymphoma [16]	Brentuximab + chemotherapy vs. chemotherapy	664 vs. 670	Neutropenia (grade 3–4): 58% vs. 45%; febrile neutropenia: 9% vs. 4%
Brentuximab vedotin	Phase 3 RCT in CD30 + Peripheral T-cell lymphoma [17]	Brentuximab + chemotherapy vs. chemotherapy	226 vs. 226	Neutropenia: 35% vs. 34%; febrile neutropenia: 18% vs. 15%; infections grade 3–4: 19% vs. 14%
Gemtuzumab ozogamicin	RCTs for AML (pooled in: [1, 27])	Gemtuzumab + chemotherapy vs. chemotherapy	622 vs. 483	Serious infection (grade 3–4): 44% vs. 47%; febrile neutropenia:24% vs. 26%

Table 6.1 (continued)

Drug	Type of study [ref]	Treatment arms	No. of subjects	Rate of infections (drug vs. comparator)
Daratumumab	5 phase 3 RCTs in newly diagnosed or relapse/refractory myeloma [38]	Daratumumab + standard treatment vs. standard treatment	Total 3547	Infection (any grade): 58% vs. 48%; pneumonia (any grade): 12.6% vs. 7.7%; neutropenia (grade 3–4): RR 1.48(95% CI: 1.17–1.88, $p = 0.001$)
Isatuximab	2 RCTs in relapsed/refractory myeloma [42, 43]	Isatuximab + standard treatment vs. standard treatment	154 vs. 153; 179 vs. 123	URTI (any grade): 28% vs. 17%; URTI (grade 3–4): 3% vs. 1% and 32% vs. 28%)
Dacetuzumab	Phase 2 RCT in relapsed non-Hodgkin lymphoma [50]	Dacetuzumab + chemotherapy vs. placebo + chemotherapy	75 vs. 76	Neutropenia (grade 3–4): 33% vs. 24%; febrile neutropenia (grade 3–4): 16% vs. 9%
Eltuzumab	Phase 3 RCT in relapsed/refractory myeloma [56]	Elotuzumab + lenalidomide and dexamtehasone vs. lenalidomide and dexamethasone	321 vs. 325	Overall infection:81% vs. 74%; lymphopenia (grade 3–4): 77% vs. 49%; VZV: 4.1 vs. 2.2 per 100 pts-years
Elotuzumab	Phase 3 RCT in relapsed/refractory myeloma [57]	Elotuzumab + pomalidomide and dexamethasone vs. pomalidomide and dexamethasone	60 vs. 57	Overall infection (all grades): 65% vs. 65%; lymphopenia (grade 3–4): 8% vs. 2%; VZV infection (all grades): 5% vs. 2%
Mogamulizumab	Phase 2 RCT in adult T-cell leukemia/lymphoma [61]	Mogamulizumab + chemotherapy vs. chemotherapy	29 vs. 24	Overall infection: 66% vs. 67%; febrile neutropenia: 90% vs. 88%; lymphopenia (grade 3–4): 97% vs. 75%; CMV infection:14% vs. 0%
Mogamulizumab	Phase 3 RCT in relapsed cutaneous T-cell lymphoma [63]	Mogamulizumab vs. vorinostat	184 vs. 186	URTI (any grade): 10% vs. 5%; pneumonia: 6% vs. 3%; cellulitis: 4% vs. 5%

ALL acute lymphoblastic leukemia, *AML* acute myeloblastic leukemia, *CMV* cytomegalovirus, *HBV* hepatitis B virus, *HL* Hodgkin lymphoma, *HSCT* hematopoietic stem cell transplantation, *HSV* herpes simplex virus, *PjP Pneumocystis jirovecii* pneumonia; RCT, randomized clinical trial; RR, relative risk; SLE, systemic lupus erythematosus; URTI, upper respiratory tract infection; UTI, urinary tract infection; VZV, varicella zoster virus

Table 6.2 Summary of risk of infectious complications and suggested management strategies (adapted from [1, 64, 65])

Agent	Risk of neutropenia/ febrile neutropenia	Risk of HSV/ VZV infection /reactivation	Risk of HBV reactivation (if used without prophylaxis)	Risk of CMV infection	Risk of PjP infection	Other infections to be considered	Recommended prophylaxis
Epratuzumab	No/no	No	Low (<1%) to moderate (1–10%)	No	No	–	HBV prophylaxis or preemptive treatment in patients at risk
Inotuzumab ozogamicin	Yes/yes	No	Low (<1%) to moderate (1–10%)	No	Yes—in ALL patients with prolonged neutropenia	–	HBV prophylaxis or preemptive treatment in patients at risk
Brentuximab vedotin	Yes/yes (low)	Yes	Moderate (1–10%)	Yes	Yes—in HL patients after HSCT	PML	HSV/VZV prophylaxis in HL patients after HSCT; CMV monitoring; HBV prophylaxis or preemptive treatment in patients at risk
Gemtuzumab ozogamicin	Yes/yes	No	Low (<1%)	No	No	Prolonged neutropenia-related infections	Standard prophylaxis in AML patients during therapy
Daratumumab	Yes/yes	Yes	Moderate (1–10%)	No	No	–	HSV/VZV prophylaxis; HBV prophylaxis or preemptive treatment in patients at risk
Isatuximab	Yes/yes	Yes	Moderate (1–10%) to high (>10%)	No	No	–	HSV/VZV prophylaxis; HBV prophylaxis or preemptive treatment in patients at risk
Dacetuzumab	Yes/yes	Possible	Possible	Possible	Possible	–	According to individual risk

Elotuzumab	Yes/yes (low)	Yes	Possible	No	No	Lymphopenia-related infections	HSV/VZV prophylaxis; other prophylaxis according to individual risk
Mogamulizumab	Yes/yes	Yes	Moderate (1–10%) to high (>10%)	Yes	Possible	Lymphopenia-related infections	HSV/VZV prophylaxis; HBV prophylaxis or preemptive treatment in patients at risk, CMV monitoring; PjP prophylaxis

ALL acute lymphoblastic leukemia, *AML* acute myeloblastic leukemia, *CMV* cytomegalovirus, *HBV* hepatitis B virus, *HL* Hodgkin lymphoma, *HSCT* hematopoietic stem cell transplantation, *HSV* herpes simplex virus, *PjP Pneumocystis jirovecii* pneumonia, *PML* progressive multifocal leucoencephalopathy, *VZV* varicella zoster virus

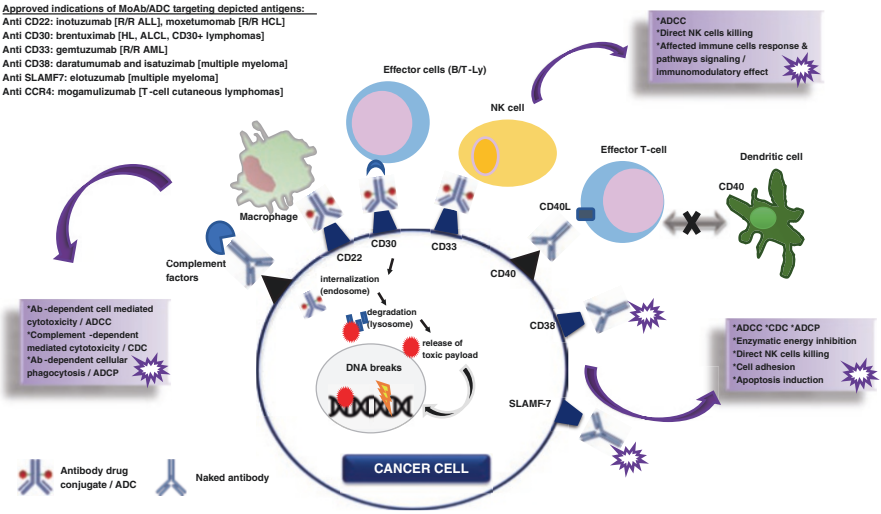

Fig. 6.1 Mechanism of action of naked and conjugated targeted monoclonal antibodies targeting CD22, CD30, CD33, CD38, CD40, SLAMF7, and CCR4. Antibodies can promote antitumor activity against cancer cells in a variety of ways: antibody-dependent cell-mediated cytotoxicity via recruitment of effector cells (ADCC), antibody-dependent cellular phagocytosis through macrophages or complement leading to cell lysis (ADCP), complement-mediated cytotoxicity (CDC), inhibition of enzymatic functions of cells via adenosine (ADP/NAD+), through NK cells with direct killing, antibody cross linking, alteration of effector cell response utilizing immunomodulating effect, via programmed cell death/induction of apoptosis. Most antibodies have multilevel activity (especially anti-CD38 and SLAMF-7). Anti-CD40 and SLAMF-7 antibodies also affect microenvironment and effective adhesion between myeloma cells or adhesion to bone marrow stroma (not shown in the figure). Major effect of ADC is to deliver toxic payload into nucleus leading to DNA disruption and subsequent cell death. *MoAb* monoclonal antibody, *ADC* antibody-drug conjugate, *R/R* relapsed/refractory, *ALL* acute lymphoid leukemia, *AML* acute myeloid leukemia, *HCL* hairy cell leukemia, *HL* Hodgkin lymphoma, *ALCL* anaplastic large cell lymphoma

CD22-Targeted Agents: Epratuzumab, Inotuzumab Ozogamicin, Moxetumomab Pasudotox

CD22 Antigen

CD22 antigen is a transmembrane glycoprotein expressed solely on mature B-cells including neoplastic blast cells (leukemia, lymphoma). Hematopoietic stem cells or other cell-lineages do not express CD22. CD22 receptor regulates B-cell functions and their responses to antigens via B-cell receptor activation and associated signaling pathways, serves as an adhesion molecule, plays important role in the migration of B-cells into gut lymphoid tissues and bone marrow, and as an important inhibitory receptor regulates induction of autoimmunity [3].

Mechanism of Action and Current Indications of Anti-CD22 Monoclonal Antibodies

The first fully humanized IgG1 MoAb targeting CD22 was epratuzumab. Upon administration and rapid internalization, epratuzumab causes phosphorylation of CD22 and downstream signaling molecules, but it does not block CD22 ligand binding, does not initiate CD22-mediated signal transduction or apoptosis, and does not demonstrate any direct cytotoxicity [4]. It has been studied for the treatment of non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), and autoimmune Sjogren's syndrome and systemic lupus erythematosus (SLE). The drug does not hold any current approved indication.

Inotuzumab ozogamicin (inotuzumab) is a humanized anti-CD22 IgG4 ADC linked to a potent cytotoxin, calicheamicin, an antibiotic product of *Micromonospora echinospora calichensis*. Upon antibody binding to CD22 antigen on the B-cell surface, the complex is internalized via endocytosis; calicheamicin is released intracellularly and by causing DNA strand cleavage leads to cell apoptosis. Inotuzumab is used for the treatment of relapsed or refractory (R/R) adult precursor B-ALL and is under investigation for the treatment of B-ALL in pediatric patients. Off-label use was studied in aggressive and indolent NHLs.

Moxetumomab pasudotox is a recombinant, genetically fused immunotoxin, consisting of variable fragment of anti-CD22 MoAb and 38-kDa fragment of *Pseudomonas* exotoxin (PE38) as an innovative, linker-less ADC. Binding of this complex to the CD22 antigen leads to internalization and toxin release, which induce a cascade of apoptosis. It is approved for the treatment of R/R hairy cell leukemia. It has been evaluated for patients with NHL, ALL, and chronic lymphocytic leukemia (CLL), but further development for these indications was terminated.

Clinical Evidence

Clinical trials with epratuzumab, which was extensively evaluated in patients with autoimmune SLE and to a lesser extend in patients with R/R lymphoid malignancies, did not show an increased rate of infectious complications [5, 6].

Monotherapy with inotuzumab (vs. standard intensive chemotherapy) in the phase 3 randomized clinical trial (RCT) in patients with B-ALL showed similar rate of neutropenia, but lower rate of grade ≥3 febrile neutropenia (~15%) and overall infections [7]. Long-term follow-up of this study confirmed a high rate of neutropenia (~45%), but a lower rate of febrile neutropenia with inotuzumab in comparison with intense chemotherapy (27% vs. 54%, respectively) and no increased risk of invasive fungal infections [8]. In combination with low-intensity chemotherapy and/or CD19 MoAb blinatumumab, inotuzumab showed a lower risk of infection in older frail patients (including death due to sepsis) than standard intensive chemotherapy [9]. Therapy with inotuzumab, as opposed to intensive chemotherapy, was associated with higher incidence of febrile neutropenia only in patients with higher percentage of blasts (>90%) in bone marrow, whereas it remained high,

irrespectively of blasts percent, with intensive chemotherapy. The grade of bone marrow leukemic involvement had no impact on the overall incidence of neutropenia and infections, including sepsis [10]. Children with R/R ALL treated with inotuzumab also had low rate of febrile neutropenia (12%) or overall infections (22% of grade ≥3) [11].

Moxetumomab pasudotox was the first recombinant antibody globally approved ADC for the treatment of R/R hairy cell leukemia. Pivotal phase 3 nonrandomized trial documented 16% grade ≥3 infections and 5% grade ≥3 febrile neutropenia [12].

Risk of Infections and Its Management

Administration of epratuzumab and inotuzumab is followed by a decrease of circulating and proliferating CD22+ B- cells for up to 12 months after the last dose. Long-term B- cell depletion was not documented after moxetumomab pasudotox. Therapy with these agents appear to cause neither significant decline of serum immunoglobulin levels nor significant increased risk of severe infections.

Similar mechanism of action to other targeted therapies focused on B-lymphocytes (like anti-CD20 MoAb, e.g., rituximab), and available clinical data may suggest the following conclusions and proposals for prevention:

- Generally, the risk of infections in patients treated with anti-CD22 agents is relatively low; usually the infection risk is determined by the underlying hematological malignancy, comorbid conditions, age, and concomitant therapy.
- Risk of infection should be individually evaluated in patients treated with anti-CD22 agents; universal antibacterial, antifungal (including anti-*Pneumocystis jirovecii*), or antiviral prophylaxis is not recommended, but prophylaxis should be individualized (e.g., patient with R/R ALL treated with inotuzumab with expected prolonged neutropenia).
- Given that anti-CD22 agents lead to depletion of all CD22+ B-lymphocytes, this therapy might be associated with reactivation of hepatitis B virus. Proper monitoring and prophylaxis is thus recommended in patients with hepatitis B surface antigen (HBsAg), and anti-HBc should be checked and confirmed by PCR DNA for HBV viral load; antiviral prophylaxis or therapy with tenofovir or entecavir-based regimens is recommended. Periodical monitoring of HBV DNA with preemptive antiviral treatment in patients who are HBsAg negative but anti-HBc-positive is also an alternative.

CD30-Targeted Agents: Brentuximab Vedotin

CD30 Antigen

CD30 is a 120-kDa transmembrane glycoprotein and a member of the tumor necrosis factor receptor superfamily. CD30 has a low level of expression in normal cells,

mainly on subsets of activated T-cells (CD4 and CD8-positive) and B-cells, monocytes, and NK cells. Its ligand, CD30L, is more widely expressed on cells of the lymphoid and myeloid lineage. CD30 expression is also ubiquitously expressed on certain malignant cells, such as on Reed-Sternberg cells, the pathognomonic diagnostic cells for classical Hodgkin lymphoma (HL), and in anaplastic large cell lymphoma (ALCL). The full biological functions of CD30 on immune system are less understood than its role in tumorigenesis; but its complex effect involves downstream signaling via nuclear factor kappa B and mitogen-activated protein kinase/extracellular signal-regulated kinase pathways as well as regulation of the balance between Th1 and Th2 responses and generation of effector and memory T-cells [13].

Mechanism of Action and Current Indications for CD30 Monoclonal Antibodies

Brentuximab vedotin (brentuximab) is an ADC composed of a human/murine chimeric anti-CD30 IgG1 MoAb conjugated via a protease-cleavable linker with the microtubule disrupting agent monomethyl auristatin E (MMAE), a synthetic derivative of a natural cytostatic pseudopeptide originally isolated from the marine mollusk *Dorabella auricularia* [14]. Upon binding to CD30 on the surface of the T-lymphocyte, the drug is internalized by endocytosis and then the proteolytic enzymes cleave linkage and monomethyl auristatin A is released in the intracellular space, binds to tubulin, and by disruption on microtubules causes cell cycle arrest. The FDA (Federal Drug Administration) and EMA (European Medical Agency) approved brentuximab for the treatment of R/R HL, for consolidation therapy in patients with HL with high risk of relapse or progression after autologous stem cell transplantation, for newly diagnosed HL in combination with chemotherapy, and for CD30+ relapsed primary cutaneous ALCL or CD30+ mycosis fungoides.

Clinical Evidence

Monotherapy with brentuximab in patients with R/R HL and ALCL in phase 2 studies showed no specific infectious complications, and incidence of grade ≥3 neutropenia in 20–29% of participants [15]. The incidence of neutropenia was higher when brentuximab was administered in combination with chemotherapy. In phase 3 RCT comparing brentuximab + chemotherapy (AVD) to standard chemotherapy (ABVD) for the treatment of advanced stages HL, brentuximab was associated with higher risk of grade ≥3 neutropenia (58% vs. 45%, respectively) and with higher incidence of febrile neutropenia (9% vs. 4%, respectively) [16]. Phase 3 RCT, which compared brentuximab + chemotherapy (CHP) to standard chemotherapy (CHOP) in patients with untreated CD30+ peripheral T-cell lymphoma, showed similar rate of neutropenia between both arms (35% and 34%, respectively), which could have been reduced by the use of primary prophylaxis with granulocyte-colony stimulating factor (13% for both arms). The study also

showed comparable rate of febrile neutropenia (18% vs. 15%) and grade ≥3 infections (19% vs. 14%) for brentuximab + CHP vs. CHOP, respectively [17]. Consolidation therapy with brentuximab in patients with high risk of relapse or progression of HL after autologous transplantation in a phase 3 RTC was associated with higher rate of neutropenia (35% vs. 12% in placebo arm, respectively) but only one case of febrile neutropenia. Treatment-related adverse events later reported by Nademanee [18] showed infections in 60% and 50% of patients treated with brentuximab vs. placebo, respectively (serious infections in 9% and 4%, respectively). Herpetic infections (VZV and HSV) were more frequent in brentuximab-treated patients than in the placebo arm (total 19 vs. 5 patients for brentuximab vs. placebo, respectively), but only once infection in each subgroup was of grade 3. VZV infections were also observed in patients on antiviral prophylaxis, but they occurred later when compared to patients without prophylaxis (median time to development of VZV from brentuximab was 200 days vs. 89 days with and without prophylaxis, respectively). Other opportunistic infections were not different between arms, and only one case of *Pneumocystis* pneumonia occurred in a patient noncompliant with recommended prophylaxis.

Severe CMV retinitis was observed after brentuximab treatment of CD30+ lymphomas. All cases were successfully treated with antivirals, but after brentuximab rechallenge, CMV infection relapsed, emphasizing the need of secondary CMV prophylaxis in case of continuation of brentuximab treatment [19]. CMV reactivation has been reported in 5 of 25 patients receiving brentuximab therapy for the relapse of HL after allogeneic hematopoietic transplantation, but only one patient presented with significant organ involvement [20]. The overall risk for CMV reactivation with brentuximab is considered low [21].

Progressive multifocal leukoencephalopathy (PML) is a rare but devastating neurological consequence of John Cunningham polyomavirus (JCV) infection in immunocompromised patients. PML after use of brentuximab has been reported in few case reports in patients with hematological malignancies. The duration of previous therapy before symptoms onset was shorter in cases of brentuximab-related PML (median of 6–9 weeks) than anti-CD20 MoAb-related PML (e.g., rituximab; median 63 weeks). The establishment of specific drug–disease causality is not easy, if even possible, because of disease-specific immune dysregulation in these patients and often sequential or concomitant use of various drugs. The exact role of brentuximab in the pathogenesis of PML is difficult to determine, but depletion of CD30-activated T-cells may reduce immune surveillance in central nervous system increasing the risk of PML [22]. A black box warning was inserted in the drug label in 2012.

There is a lack of clinical information regarding the risk of HBV reactivation in patients treated with brentuximab. However, the risk of HBV reactivation associated with brentuximab is estimated to be moderate (1 to <10%) taking other B-cell targeting agents as reference [23].

Risk of Infections and Its Management

The impact of brentuximab on immune system is poorly understood, but the effect on memory cells and impaired regulation of T/T-B cells is expected due to targeted antibody-dependent cell-mediated cytotoxicity (ADCC). Brentuximab also causes temporary neutropenia, which is especially important in patients with R/R disease and those after stem cell transplantation [21].

Recent knowledge and available clinical data offer the following suggestions and recommendations:

- The overall risk of infection in patients treated with brentuximab is similar to the risk in lymphoma patients per se. However, some increased risk may be possible in specific circumstances.
- Brentuximab-related neutropenia is a relatively common complication but carrying a relatively low risk of febrile neutropenia. Primary prophylaxis with G-CSF may be considered according to the patient's profile.
- No routine systemic antimicrobial prophylaxis is recommended; however, consider administration of anti-herpesvirus and anti-*Pneumocystis jirovecii* prophylaxis in patients receiving brentuximab for consolidation treatment after autologous hematopoietic stem cell transplantation.
- CMV monitoring is advisable in CMV seropositive patients during brentuximab therapy, especially in cases with symptoms compatible with CMV disease; in the case of previous CMV infection, secondary CMV prophylaxis is advisable if brentuximab is resumed.
- The risk of hepatitis B reactivation with brentuximab is moderate; screening for HBV is recommended before treatment in all patients with hematological malignancies; adequate management of HBsAg positive and anti-HBc positive is recommended, and these patients should receive appropriate prophylaxis.
- High alertness to PML is needed despite its rarity; the onset of neurological symptoms (except typical polyneuropathy) during brentuximab treatment should lead to drug discontinuation and appropriate diagnostic procedures.

CD33-Targeted Agents: Gemtuzumab Ozogamicin, Vadastuximab Talirine

CD33 Antigen

CD33 is a member of the sialic acid-binding immunoglobulin-like lectin (Siglec) family. While hematopoietic progenitor cells, myeloid cells, and monocytes (i.e., tissue macrophages, mast cells, and myeloid dendritic cells) express CD33, it has minor expression on granulocytes as well. CD33 antigen is expressed on the surface of leukemic blasts in more than 80% of cases of acute myeloid leukemia (AML) [24].

Mechanism of Action and Current Indications of Anti-CD33 Monoclonal Antibodies

Gemtuzumab ozogamicin (gemtuzumab) was the first to be approved by ADC for the use of patients with hematological malignancy. It is built with a humanized anti-CD33 immunoglobulin [Ig]G4 MoAb, a pH-sensitive hydrazone linker, and a calicheamicin derivative conjugated with the side chain reactive lysine residues of MoAb. The anti-CD33 antibody, lacking cytotoxic activity by itself, binds to the CD33 antigen, leading to internalization and release of the calicheamicin derivative into the leukemic cell. Initially, the drug was approved as a monotherapy for elderly patients with R/R AML. After subsequent studies in combination with chemotherapy, the drug showed excessive toxicity and was temporarily withdrawn from the market. Gemtuzumab was reapproved by the FDA and EMA after additional studies proved its efficacy and acceptable safety in 2017 and 2018. Currently, gemtuzumab is approved in newly diagnosed adult patients with CD33+ AML, in monotherapy for patients over the age of 2 with R/R CD33+ AML, and in combination with chemotherapy for CD33+ AML in 1 month or older pediatric patients (reviewed [25]). Gemtuzumab also showed promising results in patients with acute promyelocytic leukemia and is being used off-label for this indication. Among novel agents using conjugation with CD33 target, only vadastuximab talirine (SGN-CD33A) was evaluated in a phase 3 RCT. SGN-CD33A represents a novel anti-CD33 ADC conjugated to two molecules of pyrrolobenzodiazepine dimers via a protease-cleavable maleimidocaproyl-valinealanine dipeptide linker on engineered cysteine residues. This engineering technique creates a highly homogenous ADC with a controlled drug–antibody ratio, which should lead to greater stability in circulation and potentially lower off-target toxicity compared to gemtuzumab [26].

Clinical Evidence

Most clinical data on gemtuzumab come from combination studies where the agent was administered with approved anti-leukemic chemotherapies. Clinically relevant hematologic grade ≥3 adverse events in the early monotherapy trials included neutropenia and thrombocytopenia at rates of 34% and 22%, respectively. Subsequent monotherapy trials evidenced between 16% and 18% rates of febrile neutropenia and 35% and 39% rates of overall infections (reviewed [26]). Myelosuppression, notably persistent neutropenia and thrombocytopenia, remained the most common adverse event in all gemtuzumab clinical studies, including RCT. The incidence of grade ≥3 febrile neutropenia and infections ranged between 52–75% and 35–78%, respectively. Because gemtuzumab was used in combination with other antileukemic agents, the exact role of the agent in these side effects is hard to ascertain, but the duration of neutropenia, rate of infectious complications, febrile neutropenia and deaths due to infections were comparable across many clinical trials between patients treated with or without gemtuzumab [27]. The safety profile of gemtuzumab in pediatric patients did not differ from reports from adults [26, 28]. There were no specific infections reported, but one anecdotal case of PML was

documented in a patient after allogeneic stem cell transplantation who was previously treated with gemtuzumab [29]. The novel CD33-targeted agent, SGN-CD33A, has available data from clinical trials in patients with R/R and newly diagnosed AML, including phase 3 RTC. Phase 1–2 studies showed acceptable mortality rates (<10%), but profound myelosuppression was observed in virtually all patients (with a median of occurrence between 6 and 10 weeks). A phase 3 RTC (CASCADE) compared a hypomethylating agent with or without SGN-CD33A in elderly patients with newly diagnosed AML and was prematurely terminated due to high mortality rate (including fatal infections) in the SGN-CD33A arm [30].

Risk of Infection and Its Management

As CD33 is widely expressed on bone marrow cells, the cytotoxic effect of CD33-targeted drugs leads to profound myelosuppression, including frequent severe neutropenia. The incidence of infections is closely related to the depth and length of neutropenia. The expected spectrum of infections is similar to that observed in the population of patients with AML, and appropriate preventive strategies need to be implemented throughout the entire induction and consolidation therapy.

Suggestions and recommendations:

- The specific risk of CD33-targeted agents on infection is not fully established, but available data evidenced the myelosuppressive effect of gemtuzumab and new members of this group.
- Due to the well-defined risk of infections in patients with AML on therapy, standard prophylactic strategies should be administered.

CD38-Targeted Agents: Daratumumab, Isatuximab

CD38 Antigens

The human CD38 antigen is a 46-kDa multifunctional transmembrane protein that is widely expressed early in the differentiation of CD34+ stem cells and mature immune cells, including activated T and B lymphocytes, granulocytes, monocytes, macrophages, and NK cells. CD38 is an immune-modulatory molecule; it plays an important role in the transduction of activating signals mediated by major receptor complexes in a wide variety of immune cells, especially regulatory B-cells and NK cells, regulates cell adhesion, including regulation of mesenchymal stromal or myeloid-derived suppressor cells, and plays a critical part in extracellular nucleotide homeostasis. Although CD38 is essential for an effective immune response, it might also enhance the immunosuppressive potential of regulatory lymphocytes [31]. Virtually all myeloma cells express high levels of CD38 on their surface, similar to normal plasma cells, but the expression on normal lymphoid or myeloid cells is low. Therefore, CD38 represents an attractive therapeutic target especially for multiple myeloma.

Mechanism of Action and Current Indications of Anti-CD38 Monoclonal Antibodies

Daratumumab is a fully human IgG1 kappa MoAb targeting CD38, leading to elimination of CD38+ malignant cells via different mechanisms, including complement-dependent cytotoxicity, ADCC, and antibody-dependent phagocytosis. Daratumumab is approved by the FDA and EMA for the treatment of R/R multiple myeloma in adult patients, either in monotherapy or in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone, and for newly diagnosed multiple myeloma patients as part of multiple drug regimens (triplets or quadruplets).

Isatuximab is a chimeric mouse/human anti-CD38 IgG1 MoAb with different mechanisms of action as daratumumab; it mostly leads to ADCC and inhibition of ectoenzyme activity of CD38+ cells. It holds approval for R/R multiple myeloma in the combination with pomalidomide and dexamethasone, but multiple clinical studies evaluating its full efficacy are currently ongoing.

Clinical Evidence

Monotherapy with daratumumab in phase 2 studies was associated with low rate of grade ≥3 neutropenia (10%) and <1% rate of severe upper respiratory infections. As expected, its use in combination with other anti-myeloma agents showed higher incidence of infectious complications. Two pivotal studies with daratumumab in combination with doublets (dexamethasone and one other anti-myeloma agent) for the treatment of R/R disease showed comparable incidence of grade ≥3 infections in 20–30% of patients on therapy with and without daratumumab and similar rate of grade ≥3 pneumonia in 9% of patients (all arms). Neutropenia grade 3 or higher occurred in 13% and 52% and in 4% and 37% of patients treated with daratumumab versus the comparator arm, respectively. The rate of febrile neutropenia grade 3 or higher was relatively low, but slightly increased in the daratumumab arms (~6%) versus comparator arms (2–3%) [32, 33]. In patients with newly diagnosed myeloma, RCTs with daratumumab used in combination (doublets) showed that the incidence of neutropenia grade 3 or higher and infections grade 3 or higher was higher with daratumumab versus without it (up to 50% vs. ~35%, respectively, in the case of neutropenia; 32% vs. 23%, respectively, in the case of infections). Likewise, the rate of the pneumonia was higher with daratumumab (13% vs. 7% without it, respectively) [34]. Similarly, RTC with daratumumab added to triplets (dexamethasone, bortezomib, and melphalan) in newly diagnosed patients, evidenced higher incidence of infections grade 3 or higher (23.1% vs.14.7%) and severe pneumonia (11.3% vs. 4.0%, respectively) with daratumumab vs. without it [35], but the overall incidence of these complications did not differ from RTC where daratumumab was used in combinations with less agents (doublets). RTC using triplets with and without daratumumab in transplant-eligible patients showed again that daratumumab therapy had higher incidence of all infections (upper respiratory tract as the most

common), and of neutropenia grade 3 or higher (~30% vs. 15% without daratumumab, respectively), but the incidence of severe, infections grade 3 or higher was comparable (~20% in all groups, grade 3 pneumonia in 4% vs. 2% of patients, respectively) [36, 37]. A meta-analysis of five phase 3 RCTs (including 3547 patients) evaluating the incidence of neutropenia, infection and pneumonia in patients with myeloma treated with daratumumab concluded that patients on daratumumab combination regimens experienced higher risk of all grades neutropenia with an RR of 1.48 (95% CI: 1.17–1.88; $p = 0.001$) [38]. The addition of daratumumab contributed to higher incidence of infections of all grades and of infections grade 3 or higher with RR of 1.27 (95% CI: 1.13–1.44; $p = 0.02$), including pneumonia grade 3 or higher (RR 2.07, 95% CI: 1.50–2.85, $p < 0.001$) in newly diagnosed patients with multiple myeloma [39].

Isatuximab was evaluated in phase 2 studies in patients with R/R multiple myeloma with a rate of pneumonia and sepsis of 6.3% and 5.2%, respectively, in patients on monotherapy, while pneumonia was documented in 9% of patients receiving isatuximab in combination (with doublets) [40, 41]. In two RCT evaluating isatuximab in combinations (with doublets), the rate of neutropenia grade 3 or higher was around 46% on isatuximab, and although the frequency of upper respiratory tract infections of any grade was higher with isatuximab compared to the control arm (28% vs. 17% [42], it was similar for upper respiratory infections grade 3 or higher (3% vs. 1% in one study [42] and 32% vs. 28% in other study [43]).

In general, patients with multiple myeloma have sevenfold increased risk of all infections, and up to tenfold higher risk of viral infections, especially by herpesviruses (VZV) [44]. The incidence of VZV in the pivotal studies of daratumumab in R/R myeloma ranged between 2% and 5%. This observation was subsequently confirmed in various retrospective studies, where most of the reported infections were viral, including herpesvirus reactivation, CMV retinitis, enterocolitis, CMV syndrome, and HSV encephalitis. Coinfections with bacterial and viral pathogens are not unusual in the real-life setting. Daratumumab is associated with moderate (<1% to <10%) reactivation risk of HBV [45].

Risk of Infection and Its Management

Anti-CD38 agents' targets deplete also normal CD38+ immune regulatory cells, including NK cells, skew the T-cell repertoire and promote T-cells expansion (e.g., oligoclonality of CD4+ and CD8+ T lymphocytes), which leads to an ineffective antiviral innate and adaptive immunity [46]. Studies have reported an increased risk of infections in multiple myeloma patients undergoing therapy with daratumumab, with a higher rate of infections in severely immunocompromised patients: those with R/R or progressive disease, and during and after stem cell transplantation. The infectious complications associated with isatuximab in combination with standard of care therapies demonstrated minimal increase of severe toxicity to the known safety profile of the individual agents.

Still, the cumulative effect of novel agents may play a role in an increased rate of specific infections when compared with conventional treatment. The risk of infectious complications in patients with multiple myeloma should be considered during the whole disease course and close attention shall be paid to those after multiple lines of therapies.

Suggestions and recommendations:

- Considering the drug-associated risk for anti-CD38 agents, both daratumumab and isatuximab carry low-level additive risk for overall infections. Notwithstanding, better identification of patients at risk is needed, and evaluating the immunological profile and subsets of functional immune cells could serve this purpose.
- Increased risk of viral infections, especially VZV, is present in patients with multiple myeloma treated with anti-CD38 agents. Previous or concurrent treatment with corticosteroids and proteasome inhibitors may further potentiate the risk. VZV and HSV prophylaxis is recommended in patients treated with daratumumab. Antiviral prophylaxis (acyclovir or valacyclovir) to prevent VZV reactivation should be initiated within 1 week after starting daratumumab and continued for 3 months following treatment. Anti-myeloma agents may pose an increased risk for CMV reactivation, but according to the available data there is no excess of CMV infections after therapy with daratumumab and isatuximab.
- Hepatitis B reactivation risk for daratumumab is moderate. Screening for HBV is recommended before treatment for all patients with hematological malignancies and should be done before the administration of daratumumab. Adequate management of HBsAg positive and anti-HBc positive patients is recommended.
- Seasonal influenza vaccination should be encouraged in patients treated with daratumumab.

CD40 Targeted Agents: Selicrelumab, Dacetuzumab, Lucatumumab

CD40 Antigen

CD40 is a cell surface molecule of the tumor necrosis factor receptor family. Under physiological conditions, CD40 is expressed on antigen-presenting cells, for example, myeloid and dendritic cells, and is responsible for their activation and proliferation (e.g., upregulation of costimulatory molecules [CD58, CD80/86, CD70] and downregulation of immunosuppressive molecules [PD-L1]). CD40 expression can also be found on platelets, fibroblasts, epithelial and endothelial cells, and hematopoietic progenitors. The natural ligand for CD40, (CD40L), is expressed on activated CD4+ T-cells, B cells, NK cells, and on memory CD8+ T cells. The interaction between CD40 and CD40L is critical for the regulation of immune responses including antigen-specific activation of naïve B and T cells, class switching and

affinity maturation of immunoglobulins, secretion of cytokines, and development of memory cells [47]. CD40 expression was detected in various solid and hematologic malignancies (e.g., Hodgkin and non-Hodgkin lymphomas, Burkitt lymphoma, and multiple myeloma) altering immune systemic responses and allowing tumor cells escape [48].

Mechanism of Action, Approved Indications and Off-Labels Use of CD40 Monoclonal Antibodies

Few anti-CD40 MoAb were tested in patients with solid (selicrelumab) or hematologic malignancies (lucatumumab, dacetumumab), but none of these agents is currently approved or planned to enter phase 3 clinical trials. Lucatumumab and dacetumumab were evaluated in early phase studies for patients with R/R lymphomas, multiple myeloma and CLL, but further development was halted (reviewed [49]).

Clinical Evidence

Prolonged lymphocytopenia was observed after treatment with selicrelumab. During the phase 2 RCT of dacetuzumab + chemotherapy vs. chemotherapy alone in patients with R/R aggressive lymphoma, the rate of neutropenia and febrile neutropenia was higher in dacetuzumab (neutropenia grade 3 or higher of 33% vs. 24%, and febrile neutropenia of 16% vs. 9%, respectively) [50].

Risk of Infections and Its Management

The modest available data regarding the infection risk with the use of CD40-targeted agents does not allow to make firm conclusions. However, it is known that defected CD40 signaling (for instance inherited hyper-immunoglobulin M syndromes) leads to primary immune deficiency associated with high susceptibility to opportunistic infections, [51]. Theoretically, these syndromes (with their immune deficiency profile and spectrum of infections) could serve as a model to assess the risk in patients treated with CD40-targeted drugs.

Suggestions and recommendations:

- Therapy with CD40-targeted agents may be associated with an increased risk of neutropenia and infection.
- Extrapolating the data from inherited CD40 signaling deficiency syndromes (e.g., hyper-IgM syndrome), opportunistic infections such as *Pneumocystis jirovecii* pneumonia, CMV infection, invasive fungal infections, among others, should be expected. A prevention strategy (e.g., prophylaxis or preemptive therapy) is advised but, as there is scant data, individual risks need to be considered.

CD319 (SLAMF7) Agents: Elotuzumab

SLAMF7 (Previous CD139) Antigen

The glycoprotein signaling lymphocytic activation molecule (SLAMF7), previously known as cell-surface glycoprotein CD2 subset 1 or CD319, is a cell surface glycoprotein receptor and a member of the signaling lymphocyte activating molecular family. This receptor is highly expressed on plasma cells of all stages of differentiation, including malignant myeloma cells, and on NK cells. SLAMF7 is less expressed on CD8+ T lymphocytes, monocytes, and dendritic cells. The function of SLAMF7 is still not fully explained but it is suggested that it plays a role in NK cells activation and interaction between myeloma cells and their advantageous adhesion to bone marrow stromal cells. Soluble SLAMF7, sSLAMF7, further enhances the growth of myeloma cells via homophilic interaction with surface SLAMF7 and subsequent activation of the SHP-2 and ERK signaling pathways [52].

Mechanism of Action, Approved Indications, and Off-Label Use of Anti-CD139 Monoclonal Antibodies

Elotuzumab is a humanized IgG1 MoAb targeting SLAMF7. It binds to SLAMF7 receptor on the surface of plasma cells, tagging them for NK-plasma cell interaction and to SMAF7/CD16 receptors on NK cells, promoting their activation. This ADCC and NK-cell mediated cytotoxicity cause plasma cells death). Elotuzumab also suppresses sSLAMF7 and myeloma cell growth in vitro and in vivo through alteration of involved signaling pathways [52, 53]. Its efficacy in monotherapy is weak but increases significantly when used in combinations with standard anti-myeloma drugs, especially with immunomodulators. Elotuzumab is approved in combination with lenalidomide and dexamethasone or pomalidomide and dexamethasone for the therapy of R/R multiple myeloma. Ongoing clinical studies are investigating the position of elotuzumab in various clinical settings of patients with myeloma.

Clinical Evidence

Early phase 1 and 2 dose finding studies of elotuzumab in combination with other anti-myeloma agents reported lymphopenia/neutropenia grade 3 or higher, rates of upper respiratory tract infections, and febrile neutropenia/pneumonia at around 47%, 7%, and 14%, respectively [54, 55]. RCTs documented similar overall risk of infections) (adjusted for drug exposure) on elotuzumab combination with lenalidomide, dexamethasone or lenalidomide and dexamethasone alone (197 cases per 100 patient years in both groups). However, elotuzumab had higher incidence of VZV infections with respect to the comparator (4.1 vs. 2.2 cases per 100 patient-years, respectively), and lymphopenia grade 3 or higher (77% vs. 49%, respectively) [56]. Another phase 3 RCT evaluated elotuzumab with pomalidomide and dexamethasone versus

pomalidomide and dexamethasone alone, and similarly showed comparable rate of infections: 65% of all grades in both groups, adjusted per 100 patient-years of 182 vs. 230 events with and without elotuzumab, respectively. VZV infection was reported in 5% of patients treated on elotuzumab combination arm and in 2% in the comparator arm (all grade 1 or 2). While neutropenia of grade 3 or higher was more common in the control group (27% vs. 13% in elotuzumab arm), lymphopenia was noticed more with elotuzumab (grade 3 or higher of 8% in elotuzumab arm vs. 2% in the control arm, respectively) [57].

Risk of Infections and Its Management

According to its mechanism of action, the expected on-target side effect of elotuzumab is lymphopenia. However, this has not translated into significantly increased risk of infections in clinical practice. RCTs have observed slightly higher incidence) of all reported infections, but the incidence of serious infections was similar or even lower with elotuzumab. VZV infections were documented at higher frequency with elotuzumab, likely linked to its lymphopenic potential. Based on the available data, the impact of elotuzumab on the risk of infections should be commensurate with other anti-myeloma drugs.

Suggestions and recommendations:

- Acyclovir or valacyclovir should be considered for anti VZV prophylaxis in seropositive patients.
- Lymphopenia is a relatively common adverse event during the treatment with elotuzumab and could increase the risk for opportunistic infections. Therefore, increased awareness is needed (monitoring of total lymphocyte count and subpopulations of lymphocytes should be considered).

CCR-4-Targeted Agents: Mogamulizumab

Chemokine Receptor 4, CCR-4

CCR-4 is one of the 18 known human chemokine receptors and plays an important role in T-cell's migration and homing to the skin. CCR-4 is normally expressed on regulatory T cells (T_{regs}) and is considered as dominant chemokine receptor on Th2 and cutaneous lymphocyte antigen-expressing skin-homing T-cells. T_{regs} are involved in the mechanism of cancer escape from host immunity. Depletion of non-malignant T_{regs} in patients who subsequently underwent allogeneic hematopoietic stem cell transplantation was associated with higher risk of graft versus host disease and non-relapse mortality [58]. CCR-4 expression is particularly high on malignant T-cells and in cutaneous T cell lymphomas. In adult T-cell leukemia/lymphoma (ATLL), high CCR-4 expression is common. In peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphomas (CTCL), CCR-4 expression varies but positively correlates with advanced or R/R disease and with blood dissemination [59].

Mechanism of Action, Approved Indications, and Off-Label Use of CCR-4 Monoclonal Antibodies

Mogamulizumab is a first-in-class, recombinant defucosylated humanized IgG1 monoclonal antibody that targets CCR-4 and depletes CCR4-expressing cells by ADCC [60]. Mogamulizumab was initially approved in Japan for the treatment of patients with CCR4-positive ATLL and later for R/RPTCL and CTCL. FDA and EMA approved mogamulizumab in 2018 for patients with R/R mycosis fungoides or Sézary syndrome after at least one prior therapy. There are ongoing clinical trials in other subtypes of T-cell lymphomas, in solid cancer (monotherapy or in combination with, for example, checkpoint inhibitors), and in HTLV-1-associated diseases.

Clinical Evidence

There was no increased incidence of infectious complications in the initially conducted phase 2 studies with mogamulizumab. The use of primary anti-infectious prophylaxis in the initial single-arm study might had underestimated the real incidence of infections, but posterior studies did not use primary prophylaxis. Regarding hematological side effects that could impact the rate of infection, lymphopenia and neutropenia have been reported between 41–81% and around 40%, respectively. Slightly higher rate of CMV infection and CMV disease (pneumonia) were documented with mogamulizumab compared to control [61]. In the post-marketing surveillance study, CMV reactivation (viremia and/or disease) was shown to be the most common infection-related adverse event (rate of 8.3%) [62]. The results of the pivotal, phase 3 RTC in patients R/R CTCL treated with mogamulizumab or vorinostat have shown similar rate of infectious complications in both arms. The most common reported infections were upper respiratory tract and noticed in 10% and 5% of patients with mogamulizumab or vorinostat, respectively (all grade 1 and 2). The second most common infections were pneumonia (6% and 3%, respectively) and cellulitis (4% and 5%, respectively) [63]. Few case reports of HBV reactivation, fatal parainfluenza pneumonia, or disseminated mycobacterial infection have been reported with mogamulizumab.

Risk of Infection and Its Management

Targeting CCR-4 and depletion of CCR-4+ cells (T_{regs}) from T-lymphocyte population may be associated with a slightly increased risk of infection due to drug-induced lymphopenia. The contribution of CCR-4 blockade to this risk is hard to distinguish from the effect of other cytotoxic treatments and the intrinsic immune deficiency caused by T-cell lymphomas. The use of mogamulizumab in patients with autoimmune diseases is relatively contraindicated because of the increased risk of immune-mediated adverse events like myositis, myocarditis, pneumonitis, hepatitis, and hypothyroidism.

Suggestions and recommendations:

- Antiviral prophylaxis or preemptive approach should be used for prevention of CMV infection in CMV-seropositive patients.
- Screening for HBV infection should be performed before treatment and appropriate strategy (prophylaxis or close monitoring) should be considered for the individual patient according to local or international guidelines.
- Anti-herpesvirus and anti-pneumocystis prophylaxis is recommended in patients receiving mogamulizumab, reflecting the general experience in T-cell lymphoma patients.

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