Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network

Heinz Ludwig, Evangelos Terpos, Niels van de Donk, Maria-Victoria Mateos, Philippe Moreau, Melitios-Athanasios Dimopoulos, Michel Delforge, Paula Rodriguez-Otero, Jesús San-Miguel, Kwee Yong, Francesca Gay, Hermann Einsele, Roberto Mina, Jo Caers, Christoph Driessen, Pellegrino Musto, Sonja Zweegman, Monika Engelhardt, Gordon Cook, Katja Weisel, Annemiek Broijl, Meral Beksac, Jelena Bila, Fredrik Schjesvold, Michele Cavo, Roman Hajek, Cyrille Touzeau, Mario Boccadoro, Pieter Sonneveld

T-cell redirecting bispecific antibodies (BsAbs) and chimeric antigen receptor T cells (CAR T cells) have revolutionised multiple myeloma therapy, but adverse events such as cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenias, hypogammaglobulinaemia, and infections are common. This Policy Review presents a consensus from the European Myeloma Network on the prevention and management of these adverse events. Recommended measures include premedication, frequent assessing for symptoms and severity of cytokine release syndrome, step-up dosing for several BsAbs and some CAR T-cell therapies; corticosteroids; and tocilizumab in the case of cytokine release syndrome. Other anti-IL-6 drugs, high-dose corticosteroids, and anakinra might be considered in refractory cases. ICANS often arises concomitantly with cytokine release syndrome. Glucocorticosteroids in increasing doses are recommended if needed, as well as anakinra if the response is inadequate, and anticonvulsants if convulsions occur. Preventive measures against infections include antiviral and antibacterial drugs and administration of immunoglobulins. Treatment of infections and other complications is also addressed.

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Department of Medicine, Clinic Ottakring, Wilhelminen Cancer Research Institute, Vienna, Austria (Prof H Ludwig MD); **Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece** (E Terpos MD, Prof M-A Dimopoulos MD); **Department of Hematology, Amsterdam UMC, VU University, Amsterdam, Netherlands** (Prof N van de Donk MD, Prof S Zweegman MD); **Hospital Universitario de Salamanca, Instituto de Investigación Biomédica de Salamanca, Centro de Investigación del Cancer, Salamanca, Spain** (M-V Mateos MD); **Department of Hematology, University Hospital of Nantes, Nantes, France** (Prof P Moreau PD, C Touzeau MD); **Division of Hematology, University of Leuven, Leuven, Belgium** (Prof M Delforge PhD); **Cancer Center Clinica Universidad de Navarra, Pamplona, Spain** (P Rodriguez-Otero PhD, Prof J San-Miguel MD); **Centro de Investigación Medica Aplicada, Pamplona, Spain** (P Rodriguez-Otero, Prof J San-Miguel); **Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain** (P Rodriguez-Otero, Prof J San-Miguel); **Centro de investigación biomédica en red de Oncologia, Pamplona, Spain** (P Rodriguez-Otero, Prof J San-Miguel); **University College London Cancer Institute, London, UK** (Prof K Yong PhD); **Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza,**

Introduction

Treatment of patients with multiple myeloma has been revolutionised through the use of targeted immune therapies and in particular T-cell redirecting bispecific antibodies (BsAbs) and chimeric antigen receptor T cells (CAR T cells). The remarkable efficacy of BsAbs and CAR T cells in patients with relapsed or refractory multiple myeloma stimulated trials investigating their role in earlier lines of therapy, including first line.[1] In this Policy Review, we present a consensus statement from the European Myeloma Network on the prevention and management of adverse events during treatment with BsAbs and CAR T cells.

Methods

In 2022, a panel of experts from the European Myeloma Network and specialists in intensive care convened to develop a consensus on adverse event management. After a comprehensive review of the medical literature published between January, 2015, and December, 2022, a preliminary draft of the manuscript was distributed to all members of the consensus group, who were invited to comment on the proposed items and make suggestions. After the first draft had been reviewed, a further three rounds of review were done and amendments were made, until a final version was produced and approved by all authors.

BsAbs

BsAbs bind simultaneously to antigens expressed predominately on myeloma cells and to CD3 on T cells, thereby bridging both cell types. There are several BsAb formats, whereby most IgG-like BsAbs in clinical trials contain a modified fragment crystallisable (Fc) domain, which results in a longer half-life than with non-IgG-like formats without an Fc domain (eg, bispecific T-cell engagers and dual-affinity retargeting proteins). Teclistamab is approved for clinical use in relapsed or refractory multiple myeloma, and requests for approval have been filed for talquetamab and elranatamab with the US Food and Drug Administration and the European Medicines Agency, and several other BsAbs are in clinical development. Most of these antibodies target the B-cell maturation membrane antigen (BCMA), whereas others bind to the G protein-coupled receptor, class C group 5 member D (GPRC5D), or the Fc receptor-like protein 5, which are antigens that are preferentially expressed on multiple myeloma cells.

BsAbs are highly active in relapsed or refractory multiple myeloma, and their use can be associated with severe adverse events such as infections, cytopenias, hypogammaglobulinaemia, cytokine release syndrome, and neurotoxicity. Off-target effects of BsAbs are likely, including binding to normal lymphoid cells and possibly other cell populations. Talquetamab binds to GPRC5D, which is highly expressed on plasma cells but also on keratinised tissue, causing unusual on-target off-tumour adverse effects such as dysgeusia, mucositis, palmar–plantar erythrodysesthesia, nail dystrophy, and systemic rash. The adverse events observed in selected studies with BsAbs as a single agent are shown in table 1.

CAR T cells

CAR T cells are patient-derived T lymphocytes that have been genetically engineered to express a CAR

	Teclistamab (MajesTEC-1)[3]	Talquetamab (MonumenTAL-1)[3]	Elranatamab (MagnetisMM-1)[4]	Elranatamab (MagnetisMM-3)[5]	Linvoseltamab[6]	ABBV-383 (formerly TNB-383B)[7]	Alnuctamab[8]	Forimtamig (formerly RG6234)[9]	Cevostamab (NCT03275103)[10]
Target structure	BCMA and CD3	GPRC5D and CD3	BCMA and CD3	BCMA and CD3	BCMA and CD3	BCMA and CD3	BCMA and CD3	GPRC5D and CD3	FcRH5 and CD3
Number of patients	165	288	55	123 (cohort A)	167	124	68	105	160
Median follow-up, months	14·1	14·9	12·0	10·4	3·2	10·8	4·1	11·6	6·1
BsAb dose	Step-up doses of 60 μg/kg and 0·3 mg/kg, thereafter weekly subcutaneous 1·5 mg/kg	405 μg/kg sc weekly, 800 μg/kg sc every 2 weeks, and doses from 0·5 to 1600·0 μg/kg either sc or IV	Single priming dose 600 μg/kg or 44 mg followed by 1000 μg/kg or 76 mg, once weekly or once every 2 weeks	76 mg once weekly on a 28-day cycle with two step-up doses 12 mg and 32 mg during week 1	200 mg dose levels (n=87)	14 dose levels (25–120 000 μg), every 3 weeks	150–10 000 μg, with both fixed and step-up sc dosing	Intravenous dose range: 6–10 000 μg (n=51)	Single step-up dose (50–3600 μg) on C1D1, target dose (150–198 000 μg) on C1D8 ; double step-up (0·3-1·2 mg) C1D1, and C1D8 (3·6 mg), target dose (60–160 mg) on C1D15 followed by once every 3 weeks for a total of 17 cycles, unless PD or toxicity
Number of lines of therapy	5	5	5	5	5	5	4	5	6
Overall response rate	63·0%	74·1%	64·0%	61·0%	64·0%	57·0%	53·0%	71·4%	36·7%; 54·5% with toclizumab
PFS or DOR	PFS: median 11·3 months	PFS: median 7·5 months	PFS: median 11·8 months; DOR: median 17·1 months	PFS: median NR, at 9 months 63%; DOR: median NR, at 9 months 84·4%	DOR: median NR (data from abstract)	PFS: median 10·4 months	DOR: median NR	DOR: median 10·8 months	DOR: median 15·6 months
Cytokine release syndrome									
Grade 1–2	72·0%	79·0%	87·3%	56·3%	37·0%	57·0%	53·0%	82·4%	With tocilizumab 35·3%; without tocilizumab 90·7%
Grade ≥3	0·7%	2·1%	0	0	1·0%	2·0%	0	2·0%	With tocilizumab 0·4%; without tocilizumab 0·2%
ICANS or neurotoxicity grade 1–4	3·0%, all grade 1–2; neurotoxicity: 4·5%	10·7%, grade 3: 3% with IV infusion (phase 2 patients only)	0%	3·4%, all grade 1–2; 119 patients with two step-up doses	5·6% (all grades); 1·2%, grade ≥3	1·6%	3·0%, grade 1–2; PNP: 6·0%, grade 1–2	ICANS-like adverse events: 9·8%; 2%, grade ≥3	ICANS associated with cytokine release syndrome: 13·1%
Infections grade 1–4	76·4% (44·8% grade ≥3)	57·3% (16·8%, grade ≥3)	27·3%, grade ≥3	66·7% (35·0%, grade ≥3)	54·0% (29·0%, grade ≥3)	41·0%	34·0% (9·0%, grade ≥3)	60·8% (21·5%, grade ≥3)	42·5% (18·8% grade ≥3)
Thrombocytopenia grade 1–4	40·0% (21%, grade ≥3)	27·3% (20·3%, grade ≥3)	50·9% (29·1%, grade ≥3)	30·1 % (22·0%, grade ≥3)	15·0% (10·0%, grade ≥3)	25·0% (10·0%, grade ≥3)	24·0% (9·0%, grade ≥3)	31·4% (13·7%, grade ≥3)	9·8% (5·9%, grade ≥3)
Neutropenia grade 1–4	70·9% (64·2%, grade ≥3)	34·3% (30·8%, grade ≥3)	74·5% (71·0%, grade ≥3)	48·0% (48·0%, grade ≥3)	20·0% (17·0%, grade ≥3)	41·0% (35·0%, grade ≥3)	37·0% (32·0%, grade ≥3)	23·5% (11·8%, grade ≥3)	18·1% (16·3%, grade ≥3)
Anaemia grade 1–4	52·0% (37·0%, grade ≥3)	44·8% (31·5%, grade ≥3)	67·3% (50·9%, grade ≥3)	48·0% (36·6%, grade ≥3)	28·0% (24·0%, grade ≥3)	33·0% (14·0%, grade ≥3)	38·0% (25·0%, grade ≥3)	33·3% (15·7%, grade ≥3)	31·9% (21·9%, grade ≥3)

(Table 1 continues on next page)

Torino, Italy (F Gay MD, R Mina MD, Prof M Boccadoro MD); **Department of Internal Medicine, University Hospital Würzburg, Germany** (Prof H Einsele MD); **Department of Hematology, CHU de Liège, Liège, Belgium** (J Caers MD); **Department of Oncology and Hematology, Kantonsspital St Gallen, St Gallen, Switzerland** (Prof C Driessen MD); **Department of Precision and Regenerative Medicine and Ionian Area, Aldo Moro University School of Medicine, Bari, Italy** (Prof P Musto MD); **Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy** (Prof P Musto); **Department of Hematology, Oncology and Stem Cell Transplantation, Clinical Cancer Research Group, Universitätsklinikum Freiburg, Freiburg, Germany** (Prof M Engelhardt MD); **Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trial Research, University of Leeds, Leeds, UK** (Prof G Cook PhD); **Universitätsklinikum Hamburg–Eppendorf, Medizinische Klinik und Poliklinik, Hamburg, Germany** (Prof K Weisel PhD); **Erasmus MC Cancer Institute & Erasmus University of Rotterdam, Rotterdam, Netherlands** (A Broijl MD, Prof P Sonneveld MD); **Department of Hematology, Ankara University, Ankara, Türkiye** (Prof M Beksac MD); **Clinic of Hematology, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia** (Prof J Bila MD); **Oslo Myeloma Center, Department of Hematology, Oslo University Hospital, Oslo, Norway** (F Schjesvold MD); **KG Jebsen Center for B Cell Malignancies, University of Oslo, Oslo, Norway** (F Schjesvold); **IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seràgnoli Istituto di Ematologia, Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy** (Prof M Cavo MD); **Department of Hemato-Oncology, University Hospital Ostrava & Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic** (Prof R Hajek MD)

	Teclistamab (MajesTEC-1)[2]	Talquetamab (MonumenTAL-1)[3]	Elranatamab (MagnetisMM-1)[4]	Elranatamab (MagnetisMM-3)[5]	Linvoseltamab[64]	ABBV-383 (formerly TNB-383B)[7]	Alnuctamab[8]	Forimtamig (formerly RG6234)[9]	Cevostamab (NCT03275103)[10]
(Continued from previous page)									
Leukopenia grade 1–4	17·6% (7·3%, grade ≥3)	40·0% (30·0%, grade ≥3)	..	..	..	..	..	..	..
Lymphopenia grade 1–4	34·5% (32·0%, grade ≥3)	28·0% (25·9%, grade ≥3)	52·7% (51·0%, grade ≥3)	26·0% (24·4%, grade ≥3)	10·0% (10·0%, grade ≥3)	22% (20·0%, grade ≥3)	..	..	11·8% (11·8%, grade ≥3)
Hypogammaglobulinaemia (<400 mg/dL)	74·5% <500 mg/dL	87·0% <500 mg/dL*	..	..	..	14%	..	..	..
Manufacturer of drug	Janssen	Janssen	Pfizer	Pfizer	Regeneron Pharmaceuticals	AbbVie	Bristol Myers Squibb	Genentech	Genentech

Top row shows BsAbs of interest, with generic names where available, and the studies from which data were available. BCMA=B-cell maturation antigen. BsAb=bispecific antibodies. DOR=duration of response. FcRH5=Fc receptor-homolog. GPRC5D=G protein-coupled receptor, class C group 5 member D. ICANS=immune effector cell-associated neurotoxicity syndrome. IV=intravenously. NR=not reached. PD=progressive disease. PFS=progression-free survival. PNP=polyneuropathy neutralisation procedure. SC=subcutaneously. *This is based on 30 patients who received taquetamab at 405 µg dose level; in patients (n=44) on 800 µg/kg dose, the incidence was 71%.

Table 1: **Adverse events of BsAbs identified in studies including at least 50 patients**

molecule that redirects the specificity and function of T lymphocytes to recognise tumour antigens. When CAR T cells bind to their target antigen on tumour cells, they proliferate and exert antitumour activity[11] without the need for antigen processing and major histocompatibility complex restriction.[12] The most common adverse events are cytokine release syndrome and neurotoxicity, which are more frequent and often more severe than with the use of BsAbs (table 2). Neurotoxicity might occur as a toxic encephalopathy state, with a wide spectrum of neuropsychiatric symptoms. This neurotoxicity has been termed immune effector cell-associated neurotoxicity syndrome (ICANS) by the American Society for Transplantation and Cellular Therapy (ASTCT).[22] Other adverse events include infections, cytopenias, and hypogammaglobulinaemia, and can be exacerbated by lymphodepletion therapy with cyclophosphamide and fludarabine, which are usually administered for 3 days, and 2–9 days before CAR T-cell infusion.

Correspondence to:
Prof H Ludwig, Department of Medicine, Ottakring Clinic, Wilhelminen Cancer Research Institute, Vienna 1160, Austria
heinz.ludwig@extern.gesundheitsverbund.at

General measures

Patients should be screened for an active infection, proper organ and bone marrow function, and comorbidities. In patients with active infection, anti-myeloma treatment should be deferred until the infection is successfully treated or controlled. For initiation of therapy with BsAbs, patients are usually admitted for step-up dosing until the first full dose. Premedication usually includes a corticosteroid, an antihistamine, and an antipyretic. Patients should be monitored carefully for signs and symptoms of BsAb-related toxicity during the step-up phase and after the first full dose, which carries the highest risk of cytokine release syndrome. Because dosing intervals vary between different BsAbs, patient monitoring should be adjusted to fit the individual schedule. If the patient has fever, haemodynamic changes, dyspnoea or hypoxia (oxygen saturation <92% on room air), or neurological symptoms, vital signs should be checked every 4 h or more frequently.[23,24]

Fluid balance should be monitored closely, as should daily bodyweight. Assessment and grading of cytokine release syndrome should be done at least twice daily and whenever there is a change in the patient's condition. Neurological evaluation to assess CNS toxicity should include assessment of mental status, headache, and abnormal movements, and should be done every 8 h (or more frequently if changes occur).[23] After discharge, patients should be instructed to watch for symptoms (eg, back pain, rash, dizziness, chills, shortness of breath, chest pain, and neurological events) or signs (eg, tachycardia and hypotension) of cytokine release syndrome, CNS toxicity, or tumour lysis syndrome to avoid possible admission to hospital. Subsequent doses are usually well tolerated so that patients can be treated on an outpatient basis.

	Idecabtagene vicleucel (KarMMa)[13]	Ciltacabtagene autoleucel (CARTITUDE-1)[14]	bb21217 (CRB-402)[15]	P-BCMA-101 (PRIME)[16]	Zevorcabtagene autoleucel) (LUMMICAR STUDY1)[17]	LCAR-B38M 9 (LEGEND-2)[18]	ALLO-715 (UNIVERSAL)[19]	Orvacabtagene autoleucel (EVOLVE)[20]	CT103A (FUMANBA-1)[21]
Target structure	BCMA	BCMA (two binding domains)	BCMA	BCMA	BCMA	BCMA (two binding domains)	BCMA, alloCAR T	BCMA, with fully human binder	BCMA, fully human
Number of patients	128	97	72	90	102	74	52	51	103
Median follow-up, months	13·3	27·7	9·0	..	9	47·8	14·8	5·9	12·2
Cell dose	450×10^6 CAR T cells (n=54)	0·51–0·95 $\times10^6$ CAR T cells per kg	150×10^6, 300×10^6, or 450×10^6 CAR T cells	Step-up doses 0·75–15 $\times10^6$ cells per kg, later $0{\cdot}75\times10^6$ cells per kg	150×10^6 CAR T cells	0·07–2·10 $\times10^6$ CAR T cells per kg	4 dose levels (40, 160, 320, and 480 × 106); 320 × 106 selected for expansion, plus anti-CD52 antibody at 39 mg and 60 mg	300×10^6, 450×10^6, and 600×10^6 CAR T cells	$1{\cdot}0\times10^6$ CAR T cells per kg
Number of lines of therapy	5	6	6	6	4	3	8 (39 mg cohort); 6 (60 mg cohort)	6	4
Overall response rate	81%	97·9%	69% (for the dose 450×10^6: 74%)	73% in combination with rituximab and 71% with lenalidomide	92·2%	87·8%	64% (39 mg cohort), 67% (60 mg cohort)	91%	95%
PFS or DOR	PFS: median 12·1 months	PFS: median NR, at 27 months 54·9%	DOR: median 17 months	..	PFS: median NR, at 9 months 84·6%; DOR: median NR, at 9 months 86·1%	PFS: median 18·04 months DOR: median 23·26 months	DOR 8·3 months (39 mg cohort), 9·2 months (60 mg cohort)[1]	Median PFS not reached	Median PFS and DOR not reached
Cytokine release syndrome grade 1–4	96% (6%, grade ≥3)	95% (4%, grade ≥3)	75% (4%, grade ≥3)	25% (0%, grade ≥3)	90·2% (6·9%, grade ≥3)	At day 100: 91·9% (9·5%, grade ≥3)	52% (2%, grade ≥3)	2%, grade ≥3	93·2% (1%, grade ≥3)
Neurotoxicity grade 1–4	20% (6%, grade ≥3)	21·6% (12·3%, grade ≥3)	15% (4%, grade ≥3)	7% (2%, grade ≥3)	ICANS: 2% (0%, grade ≥3)	At day 100: 1·4% (0%, grade ≥3)	11% (0%, grade ≥3)	4%, grade ≥3	ICANS: 1·9% (0%, grade ≥3)
Infections grade 1–4	70%	58% (20%, grade ≥3; follow-up: 12·4 months)	..	..	29·4%, grade ≥3	9% (follow-up: 8 months in 57 patients)	59% (30%, grade ≥3)	14%, grade ≥3	..
Thrombocytopenia grade 1–4	65%	79·4% (59·8%, grade ≥3)	..	30%, grade ≥3	..	At day 100: 41·9% (18·9%, grade ≥3)	..	At day 29: 44%, grade ≥3	58·3%, grade ≥3
Neutropenia grade 1–4	94%	95·9% (94·8%, grade ≥3)	..	74%, grade ≥3	..	..	..	At day 29: 55%, grade ≥3	79·6%, grade ≥3
Anaemia grade 1–4	63%	81·4% (68%, grade ≥3)	..	35%, grade ≥3	..	At day 100: 29·7% (14·9%, grade ≥3)	..	At day 29: 21%, grade ≥3	46·8%, grade ≥3 (follow-up at 9·6 months in 79 patients)

(Table 2 continues on next page)

	Idecabtagene vicleucel (KarMMa)[13]	Ciltacabtagene autoleucel (CARTITUDE-1)[14]	bb21217 (CRB-402)[15]	P-BCMA-101 (PRIME)[16]	Zevorcabtagene autoleucel) (LUMMICAR STUDY1)[17]	LCAR-B38M 9 (LEGEND-2)[18]	ALLO-715 (UNIVERSAL)[19]	Orvacabtagene autoleucel (EVOLVE)[20]	CT103A (FUMANBA-1)[21]
(Continued from previous page)									
Leukopenia grade 1–4	..	61·9% (60·8%, grade ≥3)	..	..	..	At day 100: 29·7% (14·9%, grade ≥3)	..	..	74·7% grade ≥3 (follow-up 9·6 months in 79 patients)
Lymphopenia grade 1–4	30%	53·6% (50·5%, grade ≥3)	..	..	..	..	..	..	58·3% grade ≥3
Hypogammaglobulinaemia (<400 mg/dL) grade 1–4	21% (<1%, grade ≥3)	..	..	..	23·5%	..	..	..	..
Manufacturer of drug	Celgene	Janssen	bluebird bio	Poseida Therapeutics	CARsgen Therapeutics	Nanjing Legend Biotech	Allogene Therapeutics	Juno Therapeutics	Nanjing IASO Biotherapeutics

Top row shows CAR T-cell therapies of interest, with generic names where available, and the studies from which data were available. BCMA=B-cell maturation antigen. CAR=chimeric antigen receptor. DOR=duration of response. ICANS=immune effector cell-associated neurotoxicity syndrome. NR=not reached. PFS=progression-free survival.

Table 2: **Adverse events of CART cells identified in studies including at least 50 patients**

For patients treated with CAR T cells, the same precautions as for BsAbs apply. Patients with active HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) infection will not be accepted for CAR T cell production, a process that takes approximately 4–5 weeks to deliver transfected CAR T cells. In patients with active infection, lymphodepletion and administration of CAR T cells should be delayed until the infection is overcome. CAR T cells should be scheduled 2–9 days after lymphodepletion chemotherapy, which should be adapted (particularly fludarabine) to renal function. Patients should receive prophylaxis of infusion reactions with paracetamol, diphenhydramine, or other H1 antihistamines 30–60 mins before CAR T-cell infusion.

Adverse events and specific measures

Cytokine release syndrome

Cytokine release syndrome is a systemic inflammatory response mediated by the activation of T lymphocytes, with host monocytes and macrophages being the main source of cytokines such as IFN-γ, IL-6, and IL-10.[25] IL-6 is the predominant cytokine most frequently elevated in patients with cytokine release syndrome, with high concentrations correlating with severe cytokine release syndrome.[26] In patients treated with BsAbs, systemic cytokine release is mainly observed after the initial exposure to the bispecific CD3 antibody but can occur during subsequent step-up doses. With CAR T-cell therapy, cytokine release syndrome toxicity usually occurs within the first week after CAR T-cell infusion, and cytokine release syndrome usually peaks within 1–2 weeks after cell administration. The risk is increased in patients with high tumour burden, high treatment dose, and concomitant disease (table 3). Cytokine release syndrome usually begins with fever and constitutional symptoms such as rigor, malaise, and anorexia; other features include fatigue, chills, headache, and more severe adverse events such as hypotension, hypoxia, tachycardia, vascular leak, circulatory collapse, and organ toxicity. Fever can be high grade and persist for many days. Organ dysfunction might be secondary to hypotension or hypoxia but might also be due to the direct effects of cytokine release. Dysfunction of all major organ systems, including the heart, lungs, liver, kidneys, and gastrointestinal tract, might be observed. Every effort should be made to prevent organ dysfunction, but when it does occur, it can often be reversible if symptoms are recognised and treated in a timely manner.[23] The incidence and severity of cytokine release syndrome related to BsAb administration can be diminished with stepwise dosing, premedication with dexamethasone, premedication with tocilizumab, or temporary drug-discontinuation.[27] Several recommendations for grading the severity of cytokine release syndrome have been published, including those of the Common Terminology Criteria for Adverse Events and one developed under the umbrella of the ASTCT (appendix p 1).[22]

See Online for appendix

	Cytokine release syndrome	ICANS	Cytopenias and hypogammaglobulinaemia	Infections
Patient specific	Comorbidities; infections	Cytokine release syndrome; younger age; pre-existing neurological conditions	Reduced bone marrow function; high baseline BMPC infiltration; older age	Age; comorbidities; previous frequent episodes of infections; cytokine release syndrome; lymphopenia (B-cell and T-cell deficiency); neutropenia; hypogammaglobulinaemia (especially IgG1 and IgG3)
Disease related	Tumour burden	Tumour burden	Refractory, poorly controlled disease	Refractory, poorly controlled disease
Treatment related	Higher dose of BsAbs or CAR T cells	Intensity of lymphodepletion therapy; CAR T-cell therapy	Multiple previous lines of therapy; BCMA-targeted therapy; intensity of lymphodepletion therapy	High dose and long duration of glucocorticosteroids; TNF-α inhibition; bacterial and granulomatous infections, including tuberculosis; proteasome inhibitors; CD38 antibodies; virus reactivation (VZV, CMV); fluconazole increases risk for mould infections (aspergillosis and others)
Comments	Cytokine release syndrome occurs early after BsAb administration and usually with few days delay after CAR T-cell infusion	ICANS often is preceded by cytokine release syndrome	Multifactorial: poor patient condition, tumour burden, pre-treatment, BCMA-targeted therapy lymphodepletion	Biological age more important than chronological age; history of previous infections is a sensitive parameter for infection risk; BCMA-targeting therapies result in more pronounced B-cell depletion and normal plasma cell depletion; cytokine release syndrome is more associated with bacterial than with viral or fungal infections

BCMA=B-cell maturation antigen. BMPC=bone marrow plasma cell. BsAbs=bispecific antibodies. CAR=chimeric antigen receptor. CMV=cytomegalovirus. ICANS=immune effector cell-associated neurotoxicity syndrome. VZV=varicella zoster virus.

Table 3: **Risk factors for specific adverse events associated with treatment with BsAbs and CAR T cells**

In the KarMMa[13] and CARTITUDE-1[14] trials almost all patients developed cytokine release syndrome, predominantly of grade 1–2. Grade 3 or worse cytokine release syndrome was seen in seven of 128 patients in the KarMMa study[13] and in 4 (4%) of 97 patients in the CARTITUDE-1 study.[28] In each study, one patient died due to cytokine release syndrome. The median time to onset of cytokine release syndrome was 1 day in the KarMMa study and 7 days in the CARTITUDE-1 study, and the median duration was 5 days in the KarMMa study and 4 days in the CARTITUDE-1 study. Adverse events associated with severe cytokine release syndrome include sepsis, high fever, fatigue, myalgia, nausea, capillary leakage, tachycardia, cardiac dysfunction, liver failure, and renal failure. The severity of cytokine release syndrome has been found to correlate with tumour load[29] and CAR T-cell dose.[30] Comprehensive proteomic profiling of patients with B-cell acute lymphocytic leukaemia treated with CD19-targeted CAR T cells revealed that cytokine release syndrome is an IFN-γ-driven process with a protein signature that overlaps with haemophagocytic lymphohistiocytosis (HLH).[31] These findings fit well with the reported association of cytokine release syndrome with symptoms usually seen in macrophage activation syndrome with HLH.[32]

Prophylaxis and management of cytokine release syndrome

The risk of cytokine release syndrome in patients treated with BsAbs, and probably in those receiving CAR T cells, can be reduced by stepwise dosing.[33,34] Typical symptoms and signs are fever, fatigue, headaches, myalgias, nausea, hypotension (<90 mm Hg), hypoxia (oxygen saturation <90% on room air), and organ dysfunction. Grade 1 cytokine release syndrome can be treated with analgesics and antipyretics (figure 1). If concurrent infections cannot be ruled out as the cause of the fever, patients should be treated according to a protocol for infections. Systolic blood pressure should be maintained above 90 mm Hg, with fluid replacement. If early fever occurs within 72 h and there is no improvement with symptomatic measures, initiation of treatment with tocilizumab via a 60-min infusion is recommended. Seizure prophylaxis with levetiracetam or an alternative is recommended. Corticosteroids should be administered to patients with persistent or high grade symptoms and to patients refractory to tocilizumab. Corticosteroids induce global immunosuppression, including proliferation inhibition and cytokine secretion from CAR T cells and ancillary immune cells, especially myeloid cells.[23] Although direct comparative studies are not available, alternate IL-6 antagonist therapies (eg, siltuximab and clazakizumab) these drugs can be used for treatment of patients with cytokine release syndrome refractory to tocilizumab.[35] Low-dose vasopressor therapy should be considered if hypotension persists after adequate fluid replacement, in addition to dexamethasone 10 mg every 6 h. In case of grade 3 cytokine release syndrome with persistent hypotension, the patient should be transferred to intensive care. Addition of anakinra, an IL-1 receptor agonist, could be considered, because IL-1 has been identified as an additional potent driver of cytokine release syndrome-associated toxicity.[36,37] In the case of an insufficient response, consider increasing the dose of dexamethasone to 10 mg intravenously every 6 h; if refractory, increase the dose to 20 mg every 6 h. Consider anti-TNF antibodies such as infliximab, adalimumab, certolizumab pegol, and golimumab, or a circulating receptor fusion protein such as etanercept. In addition, inhibitors of JAK–STAT signalling, such as ruxolitinib and itacitinib, have been

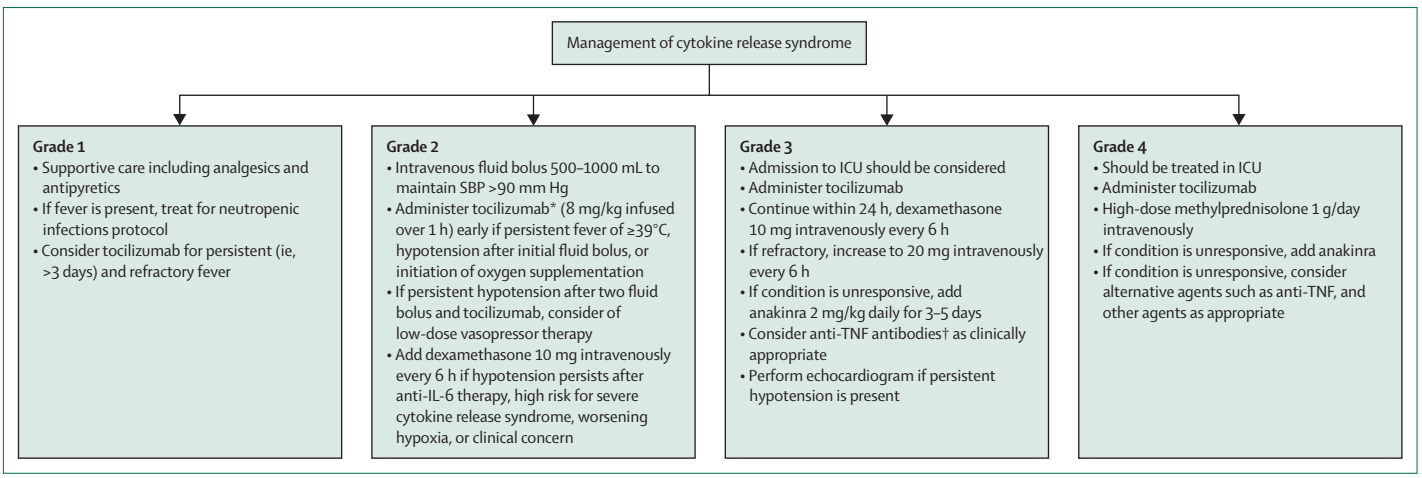

Figure 1: **Recommendations for management of cytokine release syndrome by grade of severity according to ASTCT[22]**
ASTCT=The American Society for Transplantation and Cellular Therapy. ICU=intensive care unit. SBP=systolic blood pressure. *Total single dose not to exceed 800 mg; repeat dose if no response within 6–12 h and consider corticosteroids as indicated. **Etanercept.

used in patients with poor response to other measures. The same treatments should be considered for patients with grade 4 cytokine release syndrome. These patients are usually candidates for high nasal flow oxygen, extracorporeal oxygenation, or mechanical ventilation. Some of the patients will require haemodialysis due to renal failure.

Neurotoxicity including ICANS

Neurotoxicity, including ICANS, is a disorder characterised by a pathological process affecting the CNS following immune effector therapy that results in the activation or deployment of endogenous or infused T cells or other immune effector cells. ICANS is the second most common non-haematological adverse event associated with CAR T-cell therapy, with an incidence of 2–64% for mild ICANS and 0–50% for severe ICANS. C-reactive protein concentrations usually peak before neurological symptoms occur, whereas ferritin concentrations usually peak after the onset of this complication.[38] Notably, the Immune Effector Cell Encephalopathy score (known as ICE score) is a valuable instrument for monitoring neurotoxicity (appendix p 3).[22]

Symptoms often begin with word-finding difficulties, confusion, dysphasia, expressive aphasia, and impairment of fine motor and cognitive skills, and might include somnolence, headache, disorientation, seizures, and cerebral oedema.[39] Some patients might develop cranial nerve palsy or late neurological complications such as Parkinson's disease-like movement disorders.[40] The exact biological mechanisms underlying neurotoxicity are not fully understood, but similar to cytokine release syndrome, the production of pro-inflammatory cytokines by CAR T cells, and the activation of bystander immune cells such as macrophages in the tumour microenvironment are thought to be responsible for the pathogenesis.[41] The inflammatory cytokines (eg, IL-1β, IL-6, IL-10; chemokines CXCL8 and CCL2; IFN-γ; granulocyte–macrophage colony-stimulating factor; and TNF) diffuse into the bloodstream and, eventually, lead to activation and disruption of endothelial cells, increased vascular permeability, and breakdown of the blood–brain barrier, with accumulation of cytokines and CAR T cells in the CNS. This process is accompanied by activation of resident microglial cells,[41] manifested by increased cerebrospinal fluid (CSF) concentrations of GFAP as a marker of astroglial injury and of S100 calcium-binding protein B for astrocyte activation.[42] Increased CSF concentrations of IL-6, IL-10, IFN-γ, and granzyme-B were also found to be associated with neurotoxicity.[42] This finding suggests that the accumulation of pro-inflammatory cytokines and CAR T cells in the CNS are driving ICANS. A consensus report on grading of the neurological symptoms associated with CAR T-cell therapy can be found in the appendix (p 2).

ICANS is often preceded by cytokine release syndrome, which appears to be a triggering event or cofactor for ICANS. Symptoms of ICANS usually occur after the symptoms of cytokine release syndrome have resolved, but rarely both complications can occur simultaneously. Other risk factors include higher tumour burden, which might be associated with greater spread of CAR T-cell populations and synchronous activation,[43] and pre-existing neurological diseases.[44] The intensity of conditioning therapy before CAR T-cell infusion also appears to correlate with the severity of these toxicities, probably due to higher cytokine production stimulating CAR T-cell proliferation.[45] Interestingly, older age is not associated with increased risk of severe cytokine release syndrome or ICANS.[45]

Prophylaxis and management of ICANS

Because ICANS is often associated with cytokine release syndrome, prevention of cytokine release syndrome

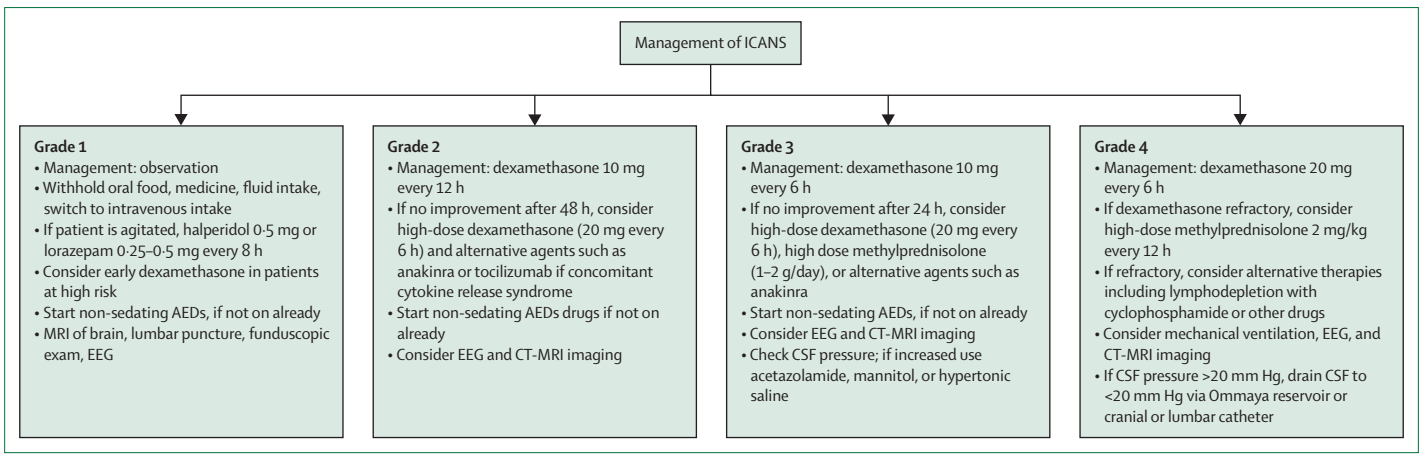

***Figure 2*: Recommendations for management of ICANS by grade of severity according to ASTCT[22]**
AEDs=antiepileptic drugs. ASTCT=The American Society for Transplantation and Cellular Therapy. CSF=cerebrospinal fluid. EEG=electroencephalogram. ICANS=immune effector cell-associated neurotoxicity syndrome.

appears to be of paramount importance, although few patients might develop ICANS without previous or concomitant cytokine release syndrome. Patients with ICANS or other neurological adverse events with risk for severe symptoms should be switched to total parenteral nutrition and medication (figure 2). These patients should be carefully assessed, including an MRI of the brain, electroencephalogram, fundoscopy, and neurological assessment. Tocilizumab is much less effective in ICANS than in cytokine release syndrome and should be administered to patients with concurrent cytokine release syndrome. Agitated patients with grade 1 ICANS might reach symptom improvement with haloperidol or lorazepam. Dexamethasone 10 mg every 6 h or methylprednisolone 1 mg/kg every 12 h should be administered to patients with grade 2 ICANS, especially if refractory to anti-IL6 therapy. If response is inadequate, increase dexamethasone dose to 20 mg every 6 h. Anakinra might be considered; however, it has only been shown to reduce ICANS in mouse models to date.[37] Patients with grade 3 ICANS should be considered for transfer to the intensive care unit. However, specific treatment options are limited and consist of maintaining or increasing glucocorticoid dose and anti-IL6 therapy in patients with concomitant cytokine release syndrome, and careful monitoring of CSF pressure and maintaining CSF pressure to below 20 mm Hg.[46] As patients' symptoms improve to ICANS grade 1, the dose can be gradually reduced. Mechanical ventilation might be required in patients whose symptoms worsen to grade 4. Patients should be monitored closely with brain MRI, fundoscopy, and CSF pressure. If patients do not respond to standard immunosuppressive therapy, lymphodepleting drugs such as cyclophosphamide or others should be considered. Patients with CSF pressure of 20 mm Hg or higher, or cerebral oedema should receive appropriate drug treatment (acetazolamide or hyperosmolar therapy with mannitol or hypertonic saline) to lower intracranial pressure and, in severe cases, surgical intervention such as insertion of an Ommaya reservoir or intracranial or lumbar catheter to monitor CSF pressure and drain CSF.

Macrophage activation syndrome

HLH, also known as macrophage activation syndrome, is a rare but potentially fatal complication of CAR T-cell therapy with hyperactivation of cytotoxic T cells, natural killer cells, and macrophages, leading to massive cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure.[47] HLH can manifest concurrent with or shortly after cytokine release syndrome, but in some cases it can manifest weeks after resolution of cytokine release syndrome, and should be suspected in patients with fever, cytopenias, hyperinflammatory markers, and especially with high ferritin concentrations (>3000 ng/mL).[48] Patients should be monitored for concurrent Epstein-Barr virus and other viral infections. Treatment is aimed at attenuating the cytokine storm with corticosteroids and tocilizumab. In case of inadequate response, anakinra can be considered because it has been shown to be effective in macrophage activation syndrome-like manifestations in a small series of patients.[49] Other treatments used for relapsed or refractory HLH include alemtuzumab and ruxolitinib, but scientific evidence for their efficacy is scarce.

Keratotoxicity of GPRC5D targeting BsAbs

GPRC5D, the target of talquetamab and some CAR T cells, is not only expressed on myeloma cells, but also on keratin expressing tissue, which might result in substantial off-target effects. Common adverse events are loss of taste, difficulties in swallowing, skin rash, nail toxicities, non-infectious fever, and anorexia. Strategies to mitigate exanthem rash include the use of emollient creams and, for oral adverse events, strategies include saliva replacement sprays and rinses when symptoms

occur.[50] Skipping a dose can also be effective in mitigating these adverse events.

Cytopenias

Cytopenias are a common complication of CAR T-cell and BsAb therapy. Grade 3 or worse neutropenias were observed in 16–64% of patients receiving BsAbs[2] and in 55–95% of patients treated with CAR T cells, and are caused by cytokines produced by the bone marrow microenvironment, which impair haematopoiesis.[51] Mandatory lymphocyte depletion before CAR T-cell therapy is another important cause of impaired bone marrow function. An algorithm originally developed for patients with diffuse large cell lymphoma[52] has now been shown to be applicable to patients with multiple myeloma undergoing CAR T-cell therapy.[53] Patients with a low baseline platelet count (<75 000 per µL), low absolute neutrophil count (<1200 cells per µL), low haemoglobin (<9·0 g/dL), high C-reactive protein (>3 mg/dL), and high ferritin (>2000 ng/mL) had lower three-lineage cell counts with long persistence, suggesting low bone marrow reserve and inflammation as key mediators of delayed recovery (high-risk group). Notably, progression-free survival has been found to be significantly shorter in the high-risk group than in the low-risk group. Another study reported any grade 3 or worse cytopenias (including neutropenia, thrombocytopenia, and anaemia) in 35 (39%) of 90 patients on the day of CAR T-cell infusion.[54] Median time to haematological recovery to grade 2 or lower cytopenia was approximately 2 months (range 1–4 months). Grade 3 or worse cytopenia was still seen in 22 (28%) of 78 patients after therapy. Patients with poor recovery were generally older, more heavily pretreated (six vs four previous lines of therapy), and more likely to have received at least one autologous stem-cell transplant. Bone marrow findings at baseline were roughly the same in both groups, but patients in the poor haematological recovery group showed a slightly higher incidence of myelodysplastic syndromes during follow-up (27% [6/28] *vs* 16% [9/72]), although this difference was not significant.

Management of cytopenias

The risk of infection increases with the severity and duration of neutropenia.[55] The use of granulocyte colony-stimulating factor (G-CSF) is recommended in patients with grade ≥3 neutropenia, but the schedule and dose of therapy should be adjusted to the individual patient's situation. Dosing every other day or three times per week can be considered, but response to therapy might be affected by the often impaired bone marrow function of heavily pretreated patients. Pegfilgrastim requires less frequent doses than filgrastim but should be used only in patients with stable disease and no risk for cytokine release syndrome. Colony-stimulating factors are not recommended for use within 14 days of CAR T-cell administration because they induce cytokine release.[56] G-CSF should also be withheld from patients at the time of initiation of treatment with BsAbs, but can be administered shortly thereafter when the risk for cytokine release syndrome has subsided. Anectotal evidence indicates that thrombopoietic agents such as eltrombopaq and romiplostin might be useful in patients with thrombocytopenia treated with BsAbs or CAR T-cells.[57] Similar considerations apply to erythropoietic agents, which have little effect during periods of infection or inflammation but might provide some benefit during periods of well controlled disease.

Hypogammaglobulinaemia

hypogammaglobulinaemia is particularly common in patients exposed to BCMA-targeted therapy, which leads to substantial depletion of B lymphocytes and normal plasma cells. In the KarMMa trial,[13] using anti-BCMA CAR T cells, 27 (21%) of 128 patients developed hypogammaglobulinaemia, and a substantially higher rate (75% [123/165]) of low IgG concentrations (<500 mg/dL) was observed with anti-BCMA BsAbs on repeated administration.[2] In another study with anti-BCMA BsAbs, 26 (70%) of 37 patients who responded to therapy developed severe hypogammaglobulinaemia (IgG concentrations <200 mg/dL).[58]

Management of hypogammaglobulinaemia

Prophylactic administration of high-dose (400 mg/kg) immunoglobulin at short intervals of 1–4 weeks is recommended in patients with low IgG concentrations (<400 mg/dL). In a 2022 study in patients treated with anti-BCMA BsAbs, immunoglobulin replacement resulted in an 80% reduction in grade 3 or worse infections compared with patients without this support.[58] This efficacy rate appears to be higher than usually observed with this treatment, but supports the recommendation of intravenous immunoglobulin as primary prophylaxis or treatment. Treatment with immunoglobulins might also be considered in patients with higher IgG concentrations and recurrent bacterial infections who do not respond to antibiotic therapy because they might not be able to mount an adequate antibody response.

Infections

Infections are common with both BsAbs and CAR T-cell therapies. The different incidences of infections in studies with BsAbs and CAR T cells involving at least 50 patients are shown in tables 1 and 2. Risk factors for infections are listed in table 3. Trials of recently approved BsAbs reported a 76·4% (126/165) infection rate with 44·8% (74/126) grade 3–4 infections in the teclistamab trial[2] and 57·3% (81/143) infection rate and 16·8% (27/143) grade 3–4 infections of patients in the 0·4 mg/kg weekly dose group of the talquetamab trial.[3] A single institution study[58] reported that most infections occurred in the respiratory tract (58%), followed by

urinary tract infections (15%), skin infections (15%), and gastrointestinal infections (8%).[59] Another retrospective analysis reported an almost equal distribution between viral (46%) and bacterial (43%) infections in patients treated with BsAbs.[58] Fungal infections were noted in 11% of patients, and cytomegalovirus reactivation was observed in 22% of patients, including two with oesophagitis.[58] Notably, 17·6% (29/165) of patients enrolled in the 2020 teclistamab study[2] tested positive for COVID-19. In a pooled analysis of 790 patients treated with BsAbs, 577 (73%) of whom were targeted for BCMA, grade 3–4 infections were observed in 205 (26%) after a short follow-up period of 4·9 months, and the number of grade 3–4 infections was lower in patients treated with non-BCMA targeted BsAbs than those treated with BCMA-targeted BsAbs (98 [17%] of 577 *vs* 59 [28%] of 213, p=0·01).[60] Another study compared the risk of infection between patients treated with BsAbs and those treated with CAR T cells.[61] 48% of those treated with BsAbs and 74% of those treated with CAR T cells had infections. The median number of infections per patient was 1·4 for BsAb and 1·5 for CAR T cells, but patients treated with BsAbs were followed up almost twice as long as those treated with CAR T cells (median 308 *vs* 161 days), skewing the results in favour of the CAR T-cells group.[61]

Two CAR T-cell preparations are approved by the European Medicines Agency and US Food and Drug Administration: idecabtagene vicleucel and ciltacabtagene autoleucel. An infection rate of 70% was found in the KarMMa trial for idecabtagene vicleucel[13] and 69% (22% grade 3–4) in the CARTITUDE-1 trial[28] for ciltacabtagene autoleucel. After a median follow-up of 13·3 months in the KarMMa study, viral infections were detected in 26 (20%) of 128 patients, bacterial infections in 17 (13%) patients, and fungal infections in 6 (5%) patients. In the KarMMa trial, the underlying pathogen could not be identified in 58% of infectious episodes.[13] Kambhampati and colleagues[62] reported their single centre study in 55 patients with BCMA-targeted CAR T-cell therapies. They noted a slightly higher incidence of viral infections (53% [29/55]) compared with bacterial infections (40% [22/55]), most of which manifested in the upper or lower respiratory tract; fungal infections were found in 3 (6%) of 55 patients, all after day 100, of which 2 (4%) were due to aspergillus and 1 (2%) was due to non-moulds. Patterns of infections varied with the time period in which they occurred. Bacterial infections typically occur during the first weeks of neutropenia and manifest as either bacteraemia or specific infection.[63] After day 30, patients become more susceptible to reactivation of cytomegalovirus and varicella zoster virus infections, and infection with other viruses such as respiratory syncytial virus and SARS-CoV-2, due to substantial lymphopenia and hypogammaglobulinaemia. Patients on BCMA-directed therapy are among the groups at highest risk for developing severe SARS-CoV-2 infections, prolonged viral shedding time, severe disease, and mortality, which in one study was 50%.[64] Although a profound response to CAR T-cell therapy is associated with reduced risk, infections—especially viral infections—remain common even in patients with complete responses.

Prevention and management of infections

Patients should be screened at baseline for HBV, HCV, HIV, cytomegalovirus, and Epstein-Barr virus infections, and carefully assessed for the presence of other infections using appropriate laboratory and imaging tests. Cytomegalovirus, Epstein-Barr virus, and HBV reactivation might occur after and during treatment exposure, and testing for these pathogens should be considered depending on the patient's individual situation. C-reactive protein and procalcitonin concentrations are also elevated in individuals with non-infectious causes of inflammation. However, normal values of these variables indicate a viral cause of a suspected infection, but are also encountered in the rare case of a patient with an intracellular bacterial infection (eg, mycobacteria). For the diagnosis of viral infections, PCR testing of the sample in question should be used rather than serum antibody testing because many patients are unable to develop an antibody response.

Preventive measures against infection include vaccination and drug prophylaxis. Several vaccines are mandatory for patients with multiple myeloma (eg, against influenza, pneumococcal disease, herpes zoster, and COVID-19) and several others are recommended for patients in specific situations (eg, against *Haemophilus influenza* and meningococci in patients with functional or anatomical asplenia, complement or properdin deficiency). Patients should be vaccinated during periods of well controlled disease.[65] There is little information about the efficacy of vaccination during treatment with BsAbs or CAR T cells, but one small study in patients treated with BsAbs found an antibody response in 6 (38%) of 16 patients to an initial dose of a COVID-19 vaccine, which improved to 75% (12/16) after booster doses.[59] Vaccination should be considered 3–6 months after completion of therapy in patients who respond to treatment. Detailed information on vaccination in multiple myeloma is available in published manuscripts on this topic.[65,66]

All patients scheduled for therapy with BsAbs or CAR T cells should receive prophylaxis against varicella zoster virus with aciclovir or valaciclovir during therapy until complete immune reconstitution, and for several months thereafter.[67] Patients with symptomatic cytomegalovirus reactivation should be treated with valganciclovir or letermovir. The options for antiviral therapy to treat infections are shown in figure 3. Ribavirin, although not approved for the treatment of respiratory syncytial virus infection, has been shown to reduce mortality in patients with haematological diseases and respiratory syncytial virus.[68] Antifungal

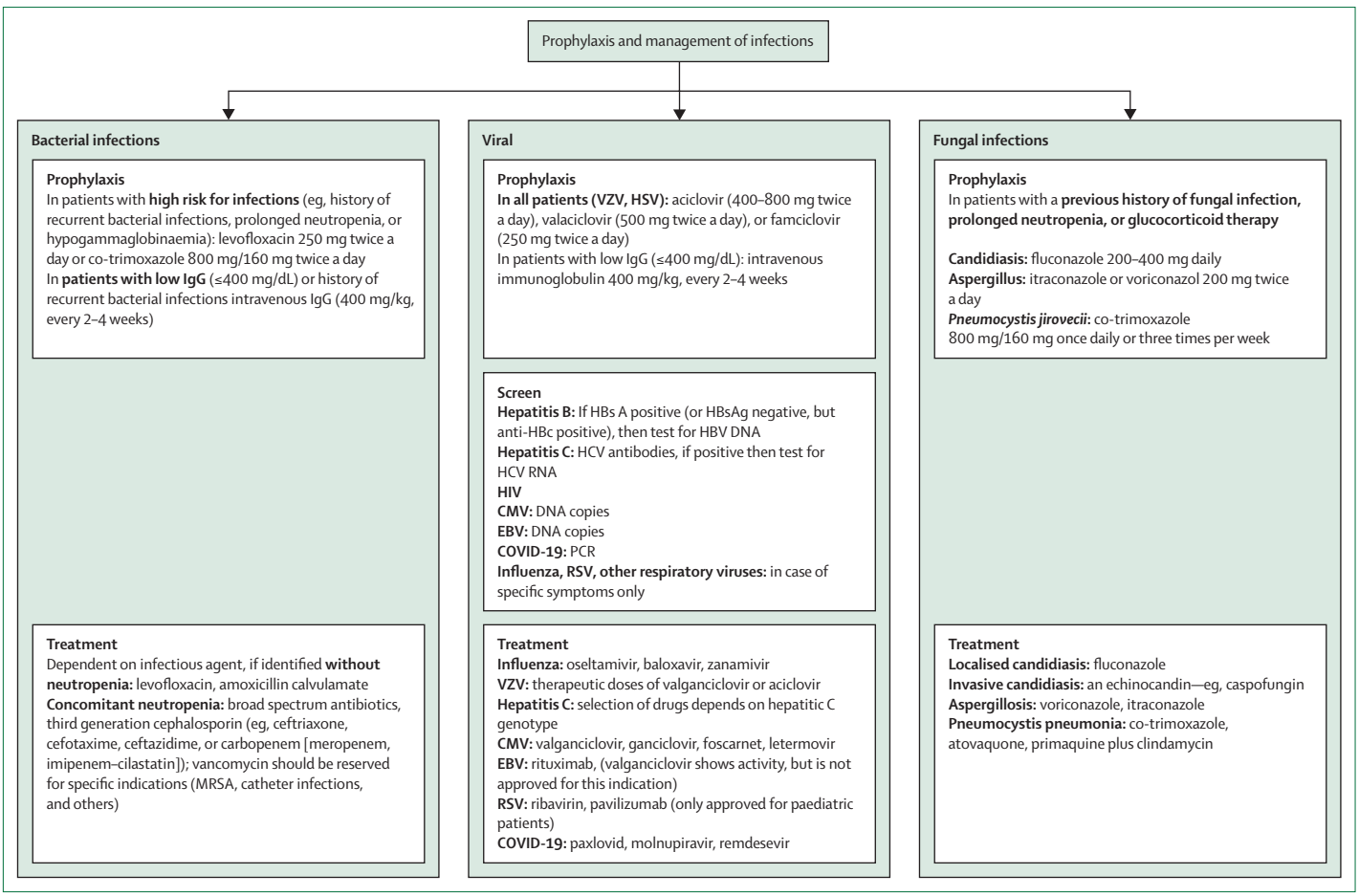

Figure 3: **Recommendations for prevention and management of infections**
CMV=cytomegalovirus. EBV=Epstein-Barr virus. HBc=hepatitis core antigen. HBs=hepatitis B surface antigen. HBV=hepatitis B virus. HCV=hepatitis C virus. HSV=herpes simplex virus. MRSA=methicillin-resistant *Staphylococcus aureus*. RSV=respiratory syncytial virus. VZV=varicella zoster virus.

prophylaxis is recommended in patients with a history of fungal infections, long-term neutropenia, and long-term corticosteroid use. Fluconazole is recommended for prevention of candidiasis, but other azoles such as voriconazole, posaconazole, and others might also be considered, particularly for prevention of Aspergillus species and especially in patients with persistent neutropenia, those with cytokine release syndrome receiving high-dose steroids, and in patients receiving tocilizumab.[69] Prophylaxis of *Pneumocystis jirovecii* with co-trimoxazole is standard of care in many protocols with BsAbs and should be administered particularly in those with low CD4 counts (<200 cells per μL). In the CARTITUDE-1 trial,[13] antibiotic prophylaxis or therapy was given to 92 (95%) of 97 patients, whereas data on antibiotic use in patients with BsAbs are not available. We recommend prophylaxis in patients in whom persistent neutropenia or hypogammaglobulinaemia must be assumed and in patients with a history of recurrent infectious episodes. The choice of antibiotic should be based on the local epidemiological situation; levofloxacin, amoxicillin, or trimethoprim–sulfamethaxol are commonly used. A limitation of fluoroquinolones is their potential spectrum of side-effects, affecting tendons, muscles, joints, nerves, and the CNS.[70] The selection of treatment for a proven bacterial infection depends on the manifestation and the infectious agent. For unknown bacterial species, diagnostic measures should be intensified, including blood and sputum cultures. In patients with febrile neutropenia, broad-spectrum antibiotics such as with imipenem–cilastatin, piperacillin–tazobactam, meropenem, or extended-spectrum antipseudomonal cephalosporins (eg, cefepime and ceftazidime) should be administered.[67] In patients with pneumonia in whom a bacterial cause is suspected, an anti-Pseudomonas β-lactam along with a fluoroquinolone or an azithromycin is a reasonable choice. CT scans of the chest can guide further diagnostic measures such as bronchoscopy and bronchoalveolar lavage. Bronchoalveolar lavage should be informative for both bacterial and viral agents as well as *P jirovecii* pneumonia. A halo

Search strategy and selection criteria

A panel of 22 members of the European Myeloma Network was invited to participate to establish a policy review on adverse events in multiple myeloma patients treated with chimeric antigen receptor T cells (CAR T cells) and bispecific antibodies (BsAbs). The first outline was decided by the publishing committee of the European Myeloma Network in September, 2022, after which the 22 panel members were selected on grounds of expertise. The panel members then evaluated and discussed the rapidly emerging data via email, which were obtained via a comprehensive literature research. We searched the electronic databases of PubMed, EMBASE, and the Cochrane Library for relevant publications. Searches were restricted to publications in English that were published from Jan 1, 2015, until Dec 1, 2022. The following search terms were used: "myeloma", "multiple myeloma", "CAR-T", "CART", "bispecific*", "BsAb*", "duobod*", "adverse event*", "safety", "CRS", "cytokine release syndrome*", "ICANS", "immune effector cell-associated neurotoxicity syndrom*", "neurotoxi*", "neutropeni*", "lymphopeni*", "thrombocytopeni*", "leukopeni*", "anemi*", "anaemi*", "hypogammaglobulinemi*", "infecti*", "macrophage", "manag*", "prevent*", AND "vaccin*". This search yielded a total of 1564 results (991 non-duplicates), which were searched for relevant information. Furthermore, we searched the abstracts of the recent meeting of the American Society of Hematology (ASH; Dec 10–13, 2022). We also searched ClinicalTrials.gov with the keywords "CAR-T cells" and "multiple myeloma", which yielded 158 search results, and we searched through a recent review on CAR T cells and ASH 2022 abstracts with the term "myeloma CAR-T" (114 matches). We further searched ClinicalTrials.gov with the keywords "bispecific" and "multiple myeloma" (35 results) and "BsAb" and "multiple myeloma" (three results), and searched through recent reviews on BsAbs[57–61], and searching through the 2022 ASH abstracts and PubMed. We selected those with at least 50 estimated enrolled patients using specific CAR T-cell or BsAb products and searched for corresponding publications on google.com, scholar.google.com, PubMed, and in the ASH 2022 and European Hematology Association 2022 abstracts. We then selected studies with publications with more than 50 patients to include in tables 1 and 2.

sign in a patient with persistent febrile neutropenia suggests invasive aspergillosis[71] but does not rule out infections by other filamentous fungi and by Pseudomonas aeruginosa. A galactomannan assay is specific for aspergillus. If *P jirovecii* pneumonia infection is suspected in a patient with dyspnoea, tachycardia, and fever, treatment should be initiated even before the diagnosis is made. Co-trimoxazole is the treatment of choice, but atovaquone and primaquine plus clindamycin are alternatives in case of allergy to co-trimaxole.[72]

Contributors

All authors participated in the development of the structure of this Policy Review. HL conducted the literature research and prepared a preliminary draft, which was discussed with PS, ET, and NvdD and modified according to the suggestions. All authors contributed to the further development of the manuscript. The final version was approved by all authors.

Declaration of interests

HL reports honoraria for lectures and for advisory boards from Celgene-BMS, Janssen-Cilag, Takeda, Amgen, Sanofi, AbbVie, and Pfizer; and research funding from Amgen and Sanofi. ET reports grants from Amgen, Janssen, GSK, Takeda, and Sanofi; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Amgen, ASTRA, BMS, GSK, Integris, Pfizer, Sanofi, and Takeda; support for attending meetings or travel from Amgen, Takeda, and Eusa Pharma; and participation on a data safety monitoring board or advisory board from BMS, GSK, Sanofi, Takeda, Eusa Pharma, Janssen, ASTRA, and Amgen. NvdD reports research support from Janssen, Amgen, Celgene, Novartis, Cellectis, and BMS; and participation on a data safety monitoring board or advisory board from Janssen, Amgen, Celgene, BMS, Takeda, Roche, Novartis, and Adaptive. 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