Adverse Event Reporting 3

Beyond maximum grade: tolerability of immunotherapies, cellular therapies, and targeted agents in haematological malignancies

Paul J Bröckelmann, Edward R Scheffer Cliff, Gloria Iacoboni, Florian Simon, Mary M Horowitz, Armand Keating, Maria-Victoria Mateos, Mohamad Mohty, Surbhi Sidana, Yuqin Song, John R Wingard, Gita Thanarajasingam

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This is the third in a **Series** of three papers about adverse event reporting. All papers in the Series are available at thelancet.com/commissions/haem-adverse-events

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University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Cologne, Germany (P J Bröckelmann MD, F Simon MD); **German Hodgkin Study Group, Cologne, Germany** (P J Bröckelmann); **Max Planck Institute for Biology of Ageing, Cologne, Germany** (P J Bröckelmann); **Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia** (E R Scheffer Cliff MBBS); **Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia** (E R Scheffer Cliff); **Department of Hematology, University Hospital Vall d'Hebron, Barcelona, Spain** (G Iacoboni MD); **Experimental Hematology, Vall d'Hebron Institute of Oncology, Barcelona, Spain** (G Iacoboni); **Department of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain** (G Iacoboni); **German CLL Study Group, Cologne, Germany** (F Simon); **Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA** (Prof M M Horowitz MD); **Princess Margaret Cancer Centre, University of Toronto,**

The increasing use of immunotherapeutic approaches, cellular therapies, and targeted agents is rapidly and profoundly changing the treatment paradigms of haematological malignancies. These novel therapies are increasingly incorporated into earlier lines of treatment. Some are administered for a fixed duration, often with curative intent, whereas others are administered chronically for disease control. The associated acute, mid-term, and long-term toxic effects can differ markedly from conventional cytotoxic chemotherapy and radiotherapy. Accumulating clinical experience and data enable identification of class-specific effects and development of consensus-based guidelines for toxicity management. In this third paper in the Series on adverse event reporting, we build on our emerging understanding of toxicity profiles of novel treatments to propose an actionable framework for improved assessment, reporting, and critical appraisal of treatment tolerability. We discuss recent insights regarding second cancers and the relevance of infectious complications, explore tolerability aspects of time-limited treatments, and suggest approaches to address gaps in tolerability assessment.

Introduction

The *Lancet Haematology* Adverse Events Commission on modernising the assessment and reporting of adverse events in haematological malignancies laid the groundwork for updated adverse event assessment and reporting beyond just aggregating maximum grades.[1,2] Although acute and long-term adverse events of cytotoxic chemotherapy and radiotherapy are well established,[3] the distinct toxicities of treatments such as chimeric antigen receptor T (CAR T) cells, other cellular therapies, bispecific antibodies (BsAbs), immune checkpoint inhibitors (ICIs), antibody–drug conjugates, and small molecule inhibitors are only now emerging. Novel cancer treatments are often initially tested in small, single-arm trials in patients with relapsed or refractory disease and few other treatment options, leading to accelerated regulatory approvals based on limited data in highly selected patient groups. The size and single-arm nature of these trials, together with often aggregated, abbreviated or incomplete adverse event reporting,[2,4] frequently precludes complete assessment of treatment-related adverse events and tolerability before using agents in routine care.

Longer follow-up of pivotal trials, larger randomised trials for full approval, retrospective academic studies, registry-based analyses, and meta-analytic approaches are increasingly used to more comprehensively evaluate patterns, prevention, and management of the toxicities of novel treatments. Through such efforts, the agent-specific and class-specific toxicity profiles of emerging therapeutics for haematological malignancies are being established (figure 1). These have informed recent consensus guidelines, for example, for the management of bispecific antibody therapy in multiple myeloma and lymphoma, targeted agents and antibody–drug conjugates in acute myeloid leukaemia, haematotoxicity following CAR T-cell therapy, and immune-related adverse events with immune checkpoint inhibitors.[5–7] These approaches are only the beginning, since important toxicities for specific drug targets or mechanisms of action often only become apparent in larger cohorts or with longer follow-up, especially for rarer events.

In this third Paper in the Series on adverse event reporting, we analyse the challenges to capturing, reporting, and managing adverse events associated with a rapidly growing range of novel therapies, with emphasis on the treatment approaches themselves. We propose an actionable framework based on the experiences and progress made in the CAR T-cell field and discuss emerging themes exemplified by selected therapeutic approaches. These include infectious complications, second primary malignancies, optimal dosing and treatment duration, issues with adverse event reporting, and attribution for combination therapies and rapidly sequenced therapies. Lastly, we identify and address challenges to ensure that the rapid introduction of groundbreaking new treatments include a comprehensive and patient-centred assessment of tolerability. Better understanding of the potential toxicities of novel treatments might not only enable their prevention, early identification, and mitigation in clinical practice, but also inform clinical decision making, improve informed consent, and refine the design of future randomised trials.

Experiences from T-cell redirecting therapies: an actionable framework

CAR T-cell therapy has revolutionised the outcomes of relapsed or refractory B-cell acute lymphoblastic leukaemia, B-cell non-Hodgkin lymphoma, and multiple

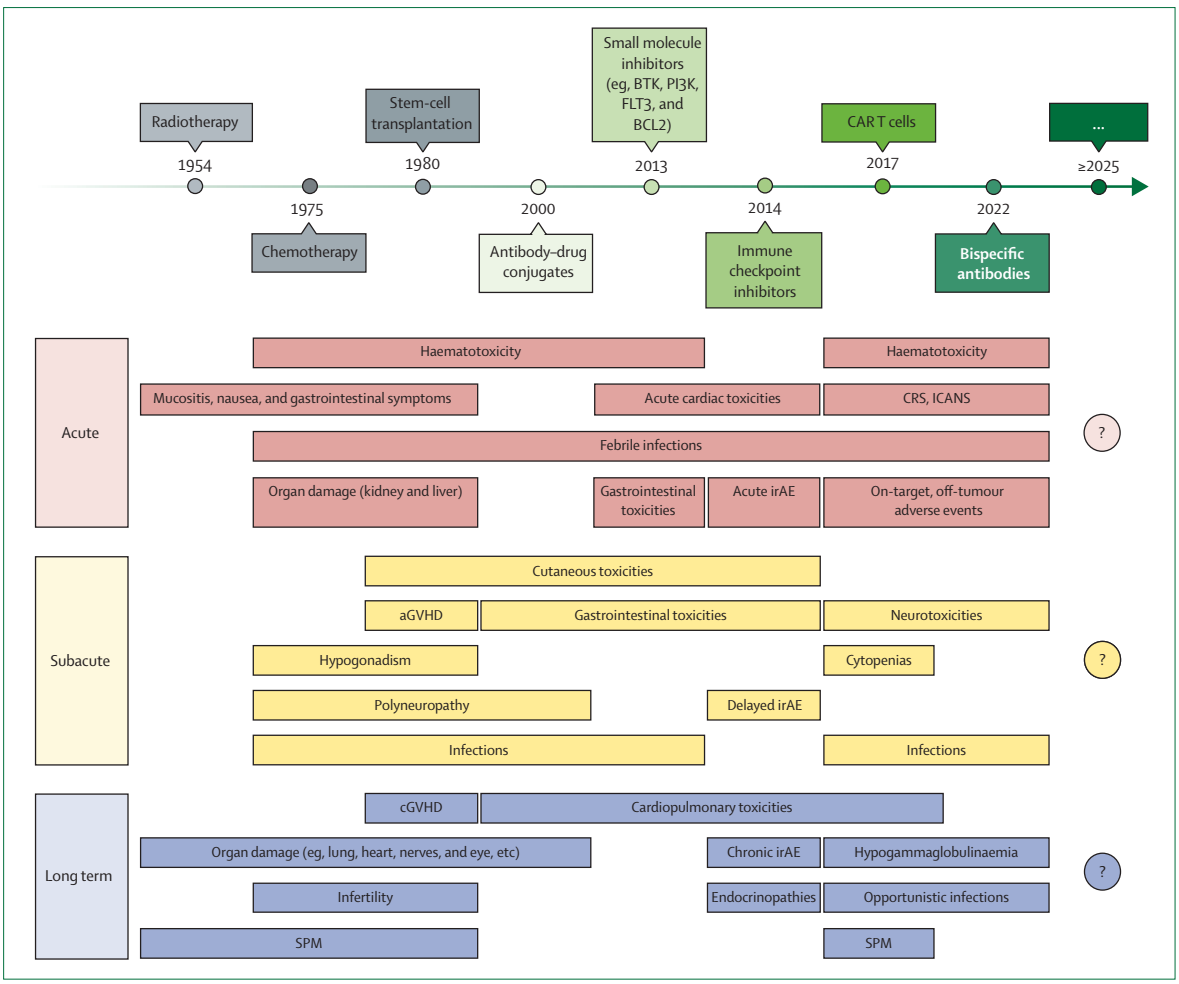

Figure 1: **Class-specific toxicity profiles of emerging therapeutics for haematological malignancies**
Selected class-specific toxicity profiles of therapeutic approaches. Acute: days to weeks after start; subacute: weeks to months after start; long-term: months to years after treatment. aGVHD=acute graft-versus-host disease. BCL2=B-cell lymphoma 2. BTK=Bruton's tyrosine kinase. CAR=chimeric antigen receptor. cGVHD=chronic GVHD. CRS=cytokine release syndrome. FLT3=FMS-like tyrosine kinase 3. ICANS=immune effector cell-associated neurotoxicity syndrome. irAE=immune-related adverse events. PI3K=phosphoinositide 3-kinases. SPM=second primary malignancies. ?=Unknown side-effect profiles. ...=Emerging novel drug classes.

myeloma. In recent years, several CAR T-cell products received regulatory approval.[8] Additionally, an array of bispecific antibodies are now available for many of the same indications as CAR T cells, and other immune effector cell-activating approaches are under development for various haematological malignancies.

T-cell redirecting strategies are associated with unique safety profiles, both in terms of acute and late adverse events. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) are the most common acute adverse events after CAR T-cell infusion, with incidence and severity dependent on the specific product and disease.[9] Initial reports of these adverse events used heterogeneous grading systems, which precluded cross-trial and real-world data comparisons and hampered the development of consensus management strategies. In 2018, experts from different institutions, supported by the American Society for Transplantation and Cellular Therapy, established uniform definitions and consensus grading systems for these acute adverse events, which led to assessment standardisation in clinical trials and real-world studies;[10] an excellent example of harmonisation across diseases, CAR T-cell products, institutions, and registries.

Another effort to unify acute adverse event definitions, grading and management addressed immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS). A multidisciplinary expert panel developed a consensus grading system and treatment options for IEC-HS.[11] Additionally, there are disease-specific recommendations, for example from the International Myeloma Working Group,[5] addressing the increasing complexity of applying novel therapeutic agents in routine clinical practice. Similarly, the growing number of approved bispecific antibodies prompted consensus strategies for mitigation and management of

Toronto, ON, Canada (Prof A Keating MD); **Hematology Department, Hospital Universitario de Salamanca-IBSAL, CIBERONC and Centro de Investigación del Cáncer, IBMCC, Salamanca, Spain** (M-V Mateos MD); **Department of Haematology, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France** (Prof M Mohty MD); **Stanford University School of Medicine, Stanford, CA, USA** (S Sidana MD); **Key Laboratory of Carcinogenesis and Translational Research, Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China** (Y Song MD); **Division of Hematology/Oncology, University of Florida College of Medicine, Gainesville, FL, USA** (Prof J R Wingard MD); **Division of Hematology, Mayo Clinic, Rochester, MN, USA** (G Thanarajasingam MD)

Correspondence to:
Dr Paul J Bröckelmann, Department I of Internal Medicine, University Hospital of Cologne, 50937 Cologne, Germany
paul.broeckelmann@uk-koeln.de

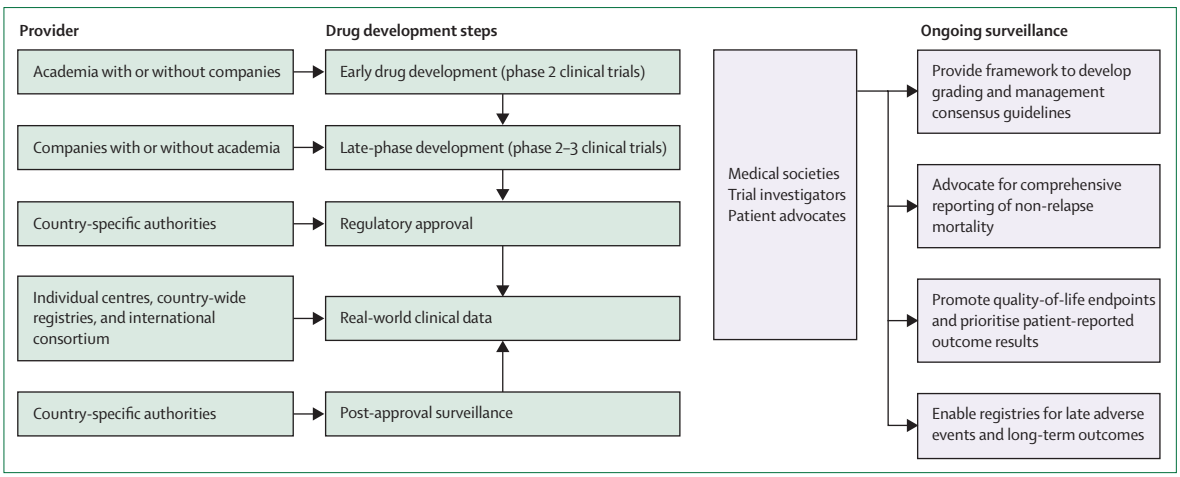

Figure 2: **Framework for ongoing surveillance and appraisal of tolerability during the drug development process**

acute adverse events in the setting of off-the-shelf products with distinct cytokine release syndrome and ICANS profiles.[6,7] Heterogeneity in prophylaxis and early intervention strategies for cytokine release syndrome and ICANS in bispecific antibody trials pose ongoing challenges. The precise recommendations regarding acute adverse events after T-cell activating therapies developed by interdisciplinary international academic consortia enable more specialised and harmonised patient management, as well as adverse event assessment and reporting, and should be promoted.

Acute adverse events after CAR T-cell infusion are well documented, but there is a paucity of data regarding long-term toxic effects. Pivotal trials mainly focus on acute adverse events and, in follow-up publications, on updated efficacy. Safety reporting is generally limited to serious or life-threatening late adverse events and is often missing detailed information. Mild or moderate late or long-lasting toxic effects are frequently overlooked, and uncommon toxicities, even if serious, potentially underreported. Outside of clinical trials, the responsibility for documentation and reporting of long-term follow-up after CAR T-cell infusion is not clearly defined. To consistently capture and report the full spectrum of late adverse events outside clinical trials, partnership and close interaction between the infusion sites and referring centres should be encouraged. Hypogammaglobulinaemia, infections, and cytopenias (ie, immune effector cell-associated haematotoxicity) have been identified as more common late adverse events.[12–14] Focusing on the latter, there were efforts to better understand the underlying pathophysiological mechanism and establish risk factors for its occurrence.

The CAR-HEMATOTOX score was an international collaborative effort to build a risk stratification model for B-cell non-Hodgkin lymphoma based on five parameters, including bone marrow reserve and inflammatory status at the time of lymphodepleting chemotherapy (platelet count, absolute neutrophil count, haemoglobin, C-reactive protein, and ferritin).[15] This score was independently validated in other haematological cancers,[16,17] addressing the need for disease-level data in predictive models. Initial studies provided cytopenia grading according to the Common Terminology Criteria for Adverse Events (CTCAE).[18–20] Recently, a dedicated task force including experts and representatives from the European Hematology Association and European Society for Blood and Marrow Transplantation was established to define, grade, and propose management recommendations for this adverse event, now termed immune effector cell-associated haematotoxicity.[21,22] The work of these task forces is another example of medical societies providing the necessary framework to reach international consensus, suitable for adoption in clinical trials and real-world reports, allowing future comparisons of cytopenia rates and severity after CAR T-cell therapy to be standardised across different settings. Immune effector cell-associated haematotoxicity can be among the most challenging late adverse events to manage; the risk of non-relapse mortality after CAR T-cell therapy is mainly due to infections, as established in a recent large meta-analysis of over 7500 patients.[23] Evaluating a well established, clinically relevant read-out, initially established in the stem-cell transplantation field, this analysis highlights the need to carry out a thorough reporting of non-relapse mortality, to better understand patterns of treatment-associated mortality.

In 2023, reports of second primary malignancies, initially T-cell lymphomas, developing in CAR T-cell recipients, prompted a rapid announcement and classwide boxed warning from the US Food and Drug Administration (FDA).[24] At the same time, multiple, comprehensive investigations from academic groups confirmed the low frequency of these T-cell lymphomas; however, investigations into the causes of therapy-related myeloid neoplasms are ongoing.[25–31] In many cases, it was not possible to assess the degree of

causality between the infused CAR T cells and second cancer, due to the absence of stored tissue or blood samples. This absence of biomaterial highlights the importance of collecting pretreatment samples before genetically modified treatments, to aid characterisation of second primary malignancies and inform our understanding of their nature and potential causal factors.

Overall, the experience from the CAR T-cell journey so far can provide a potential conceptual framework for understanding the tolerability of novel therapies in general. This framework includes vigilance for expected (ie, predicted from early-phase clinical trials) and unexpected adverse events, development of uniform standards for reporting such adverse events through international consensus, regular reappraisal with growing experience, and the systematic collection of longitudinal real-world data. Importantly, although the development of this framework was largely led by academia, early and close collaboration with other stakeholders including medical societies, patient advocates, industry, and regulatory authorities is crucial (figure 2).

Increasing the precision and speed of toxicity identification and mitigation: lessons from recent trials

Many aspects of modern drug development can make it challenging to accurately and swiftly identify toxic effect signals of novel therapeutics. The rapidity of drug development in haematology is advantageous in that it enables fast access to novel agents. However, the use of preliminary approval pathways, such as accelerated approval in the USA and conditional approval in Europe, means that novel treatments are increasingly available as standard therapies after only single-arm trials.[32] In single-arm trials in patients with exposure to multiple previous therapies, it can be very challenging to know when to attribute an adverse event to the investigational agent.[33] Frequently, clinical trial reports try to distinguish between treatment-related and treatment-emergent adverse events when the causality of the adverse event is uncertain. For example, in the placebo groups of two large double-blind randomised controlled trials, almost half the of adverse events were attributed to the study drug (ie, the placebo).[34] Ideally, presentations and manuscripts of clinical trial data should report adverse events in as much detail as is feasible, to allow readers to infer the possible attribution, and these should be reported cautiously until randomised trials are better able to establish causation. Ultimately, it is often only a difference in frequency that can suggest a causal effect.

Other challenges impeding early identification of adverse events include that, in many cases, only adverse events occurring in over 5% of patients are reported. Rarer events, which might nevertheless be clinically very relevant, might therefore not be reported at all. Sometimes, often only adverse events identified as adverse events of interest are reported with sufficient detail. For example, although rates of pyrexia—the true clinical significance of which is uncertain—are frequently reported, rates and details of documented infections might not be. Early presentation of clinical trial results can mean that delayed-onset toxic effects are not yet apparent. Examples of potentially delayed-onset toxic effects include ventricular arrhythmias and sudden death on ibrutinib,[35] parkinsonism after BCMA-targeted CAR T cells,[36] and treatment-related neoplasms with lenalidomide in multiple myeloma.[37] Requirements for timely reassessment and follow-up publication of intermediate and long-term safety results should be implemented (appendix p 1).

See Online for appendix

Furthermore, increasing use of surrogate endpoints such as response rate, measurable residual disease negativity, and progression-free survival, which do not capture non-fatal toxicity, as the primary endpoints of early phase trials means that toxicity signals can be obscured.[38,39] For example, after many clinical trials across a range of lymphoid malignancies and many years on the market, almost all approved indications for four P3IK inhibitors were withdrawn due to unfavourable safety profiles, especially from infections.[40] Similarly, ibrutinib's mantle cell lymphoma indication was withdrawn by the FDA due to the results of the SHINE trial;[35] despite a 27·7 month improvement in median progression-free survival, there was no overall survival improvement, in part due to increased toxicity in the intervention group, including infections. In the BELLINI trial of venetoclax in patients with multiple myeloma, despite improved overall response rate and progression-free survival, overall survival was worse in the intervention group, also probably due to increased infections.[41] Immune checkpoint inhibitors in combination with pomalidomide also led to increased treatment-related deaths and worse overall survival in patients with multiple myeloma.[42]

Although some clinical studies assess patient-reported outcomes (PROs), there is a lack of prioritisation on the robust collection of PROs by investigators and sponsors in haematological malignancies research, an important point that the second paper of this Series elaborates on. Endpoint selection can be particularly challenging in myeloproliferative and myelodysplastic syndromes where quality of life (QoL) assessment is especially nuanced: drugs for low-risk myelodysplastic syndromes, such as luspatercept and imetelstat, epitomise the need for patient-centred endpoints. The former can sometimes increase fatigue even when it improves haemoglobin,[43] and the latter requires a monthly intravenous infusion to reduce transfusion requirements, illustrating the need for evaluating the net effect on QoL.[44] In addition to continuing to report and use overall survival as the ultimate safety and efficacy endpoint, we recommend systematic collection and early reporting of PROs, preferably already together with the primary publication.

Additionally, analysis on the correlation between PROs, treatment decisions, patient compliance, and survival outcomes, as discussed in the second paper in this Series, are crucial.

A multi-pronged strategy is needed from trial investigators, sponsors, and regulators to enable earlier identification and mitigation of adverse events related to novel therapies. Increased use of randomisation, where possible also in early phase trials,[45] to optimise dose, duration, treatment combinations, and treatment strategies, will enable better toxicity attribution and improve the design of phase 3 trials. More frequent use of blinding will also improve the robustness of adverse event assessment—for example, the ASC4FIRST trial of asciminib in newly diagnosed chronic myeloid leukaemia was open label, even though it tested oral therapies, making the comparison of toxicities potentially biased.[46] Improved, more comprehensive, and standardised reporting of adverse events in published clinical trial datasets will allow investigators and clinicians to better appreciate the full toxicity profile of novel agents. Earlier data sharing (eg, following accelerated approval of a product) will enable rigorous secondary analyses.

Of note, the only regulatory agency that reviews individual patient data is the FDA; these data can be important in detecting irregularities in clinical trial conduct and data assessment. Ideally, more data would be made available to clinicians, and more resources allocated to conduct secondary analyses of aggregated class-wide data. Although meta-analytic approaches are useful for this purpose, meta-analyses are frequently limited by lack of granularity of reported data and heterogeneity of trial designs and patient groups. Currently, it is cumbersome or impossible for researchers to gain access to large volumes of individual patient data. Efforts such as the Yale University Open Data Access (YODA) project are poised to improve access by establishing mutually beneficial partnerships with all data partners, although access through this platform is currently restricted to specific drugs and there is often some delay between publication of trial results and access to data.

Real-world analyses are an important tool to identify safety signals after approval of a novel therapy. Informed by real-world practice, *Pneumocystis jirovecii* prophylaxis and immunoglobulin replacement are now increasingly implemented in clinically vulnerable patient groups receiving bispecific antibodies, although this was not the case in early phase studies.[47] Similarly, earlier and more aggressive treatment of cytokine release syndrome and ICANS (and the safety of corticosteroid use post-CAR T-cell therapy) derives largely from post-marketing real-world evidence generation, as has the avoidance of bendamustine before apheresis for CAR T-cell production. However, registry and real-world analyses can vary in quality, and there can be substantial delay between a product's availability and emergence of this evidence. This analysis could be improved by increased regulatory requirements for post-marketing registry and safety studies, as has been done for CAR T-cell therapies, increased funding to generate high-quality independent real-world evidence and reducing bureaucratic barriers to accessing real-world data.

Emerging challenges of infectious complications and their prophylaxis

Although important and potentially life-threatening, only 10% of non-relapse mortality after B-cell directed CAR T-cell therapy was attributable to cytokine release syndrome (5%) and ICANS (5%) in a recent large meta-analysis of 574 non-relapse deaths occurring in 7604 patients. In contrast, most of such deaths were attributed to infections (51%), including COVID-19 (53% of infection-related deaths with reported pathogen), bacterial (21%), fungal (19%), or other viral (5%) pathogens. Importantly, death due to infections was significantly higher in real-world datasets than in clinical trials (407 [65%] real world *vs* 167 [59%] trial non-relapse death, $p<0\cdot001$). This observation was even after accounting for CAR T-cell product and underlying disease and excluding COVID-19-related deaths, suggesting a class-specific effect of very high relevance to clinical practice, especially in a less selected, real-world patient population.[23]

A recent meta-analysis reported infectious complications in 44% and infections of grade 3 or worse in 20% of 2228 patients with lymphoma receiving anti-CD20 bispecific antibodies.[48] Fatal infections occurred in 3% of patients, mostly due to viral (41%; with 91% of viral infections of these due to COVID-19), fungal (6%), and bacterial (5%) pathogens. No relevant differences were observed with regards to bispecific antibody type, disease entity, or line of treatment, supporting a class-specific effect.[48] Interestingly, infectious complications appear higher after BCMA-directed versus GPCR5D-directed bispecific antibody therapy in multiple myeloma (grade 3 or worse; 25% of 976 BCMA patients *vs* 20% of 501 non-BCMA patients, $p<0\cdot01$).[49] Additionally, emerging data indicates higher severe infection risks in patients with multiple myeloma receiving BCMA-targeted therapy with bispecific antibodies (40%) versus CAR T cell (26%) or antibody–drug conjugates (8%).[50] Infections appear to be associated with hypogammaglobulinaemia (IgG <400 mg/dL) after bispecific antibodies and neutropenia after CAR T-cell treatment.[50] This finding is supported by evidence that immunoglobulin replacement substantially reduces infections with bispecific antibodies.[47] Mechanistically, this observation hints at sustained B-cell deficiency and impaired T-cell function with bispecific antibodies (potentially due to repeated stimulation[51]) and effects of bridging or lymphodepleting chemotherapies, or both, as well as sustained haematotoxicity after CAR-T cell therapy.

Consistent across recent meta-analyses is the high proportion of patients with infections, including grade 3

or worse infections or fatal infections without cause or pathogen reported, and the scarcity of data on anti-infective prophylaxis.[23,48] Apart from B-cell directed treatment, infectious complications are relevant also with small molecule inhibitors targeting BTK, PI3K, or JAK, as well as anti-inflammatory drugs, including tocilizumab, anakinra, and high-dose steroids, frequently used to treat side-effects of immunotherapies.[52] Improved reporting from clinical trials and comprehensive registries are essential to devise and execute prophylactic, diagnostic, and therapeutic strategies that reduce the morbidity and mortality associated with these increasingly used therapeutics.[53] Earlier sharing of detailed clinical trial data would enable secondary analyses to better understand the nature of infections and potentially expand prophylactic measures for patients with prolonged neutropenia or functional aplasia after cytotoxic therapy.

Considerations for earlier lines of treatment and curative-intent therapies

Encouraged by promising efficacy and side-effect profiles that are often distinct from conventional cytotoxic therapies, novel therapeutic approaches are being rapidly incorporated into earlier lines of treatment. A careful evaluation of risks and benefits is required, especially when administering treatment with curative intent. With initial data from small numbers of heavily pretreated patients with short follow-up, rare or delayed onset adverse events might be substantially underestimated. Additionally, since initial evaluations of novel drugs are frequently in clinical settings with few or no alternatives, physicians, patients, and regulators might be inclined to accept substantial side-effects if they come with sufficient efficacy. In contrast, patients treated in earlier lines of therapy are usually fitter (and might have fitter T cells) due to reduced exposure to previous therapy, different disease biology, and cancer stage. They might also differ in age, sex, ethnicity, comorbidities, concomitant medications, or lifestyle factors, with variable effects on toxicity risks. These aspects influence experience and judgment of side-effects from a patient's perspective, and could result in a very different toxicity profile than previously reported (figure 3). Ultimately, the patient perspective on what is worthwhile is valuable.[54] Although emerging data suggest an increased rate of neurological side-effects post-BCMA–CAR T-cell therapy,[36] a small risk of parkinsonism might be much more acceptable to a person aged 79 years who has previously had five lines of anti-multiple myeloma therapy than in a person aged 45 years who is treatment naive.

Similarly, with considerable non-relapse mortality attributable to infections, but also second primary malignancy or cardiovascular events,[23] earlier use of CAR T needs to be monitored carefully. For most second primary cancers, the exact role and contribution of CAR T-cells remains unknown, and further study is crucial.[26] Most of the 22 cases of post-CAR T-cell therapy T-cell lymphoma described to date have not been assessed for the CAR vector.[30,55] Overall, T-cell lymphoma only accounts for a small minority of second primary malignancies. Second primary malignancies occurred in 4·3% of CAR-T recipients according to a recent analysis of the FDA Adverse Event Reporting System (FAERS),[56] with most being myeloid (52%; myelodysplastic syndromes, or acute myeloid leukaemia) or solid cancers (44%).[26] At this time, due to the limited follow-up available for most trials, we are only able to assess early second primary malignancies and careful interpretation and discussion is essential. With a 3-year cumulative incidence rate of 9%, the risk of second primary malignancy is likely to be outweighed by the potentially life-saving benefit of CAR T-cell therapies, at least in patients with relapsed or refractory aggressive disease.[26,29] This question remains unanswered in the first-line setting, although randomised trials are currently underway (eg, NCT05605899 and NCT05257083).

Recently, striking results were reported from the GHSG HD21[57] trial, using the antibody–drug conjugate brentuximab vedotin (PET-guided BrECADD), and the US S1826 trial, which incorporated anti-PD1 antibody nivolumab (N-AVD) into first-line treatment of advanced-stage Hodgkin lymphoma. In this highly curative setting, carefully evaluating persisting and late effects versus a previous standard of care is crucial. In the HD21 trial, reduced treatment-related morbidity was reported as a

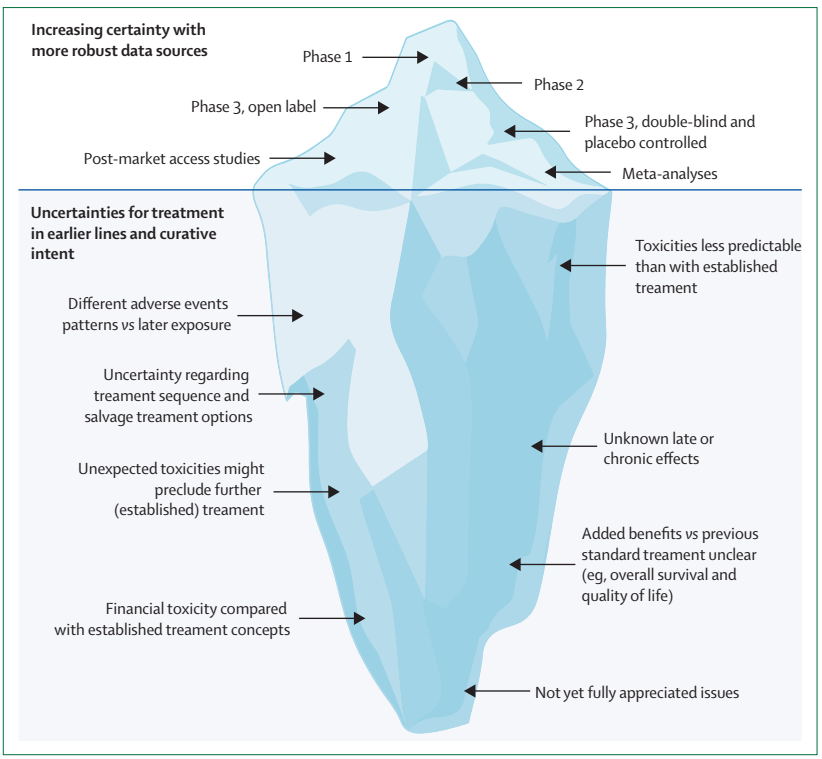

Figure 3: **The iceberg of uncertainty when using novel treatments in curative intent and in earlier lines of treatment**

coprimary endpoint[57] and secondary endpoints, such as preserved gonadal function[58] and improved QoL by PRO,[59] further substantiated the tolerability of BrECADD. For the patients treated with nivolumab, poorly predictable immune-related adverse events were of concern, since they might result in persistent organ damage, requiring life-long hormone replacement.[60] Although these combinations have yet to receive regulatory approval, they already feature in guidelines. It will be important to carefully evaluate long-term tolerability in large patient cohorts treated in the community setting.

Optimal dose and fixed duration treatment: could less be more?

Dose and treatment schedule of novel drugs are initially usually established through a maximum tolerated dose step-up design, assuming higher efficacy with increased exposure. Analogous to chronic myeloid leukaemia, where excellent disease control is achieved through continued monotherapeutic kinase inhibition, other small molecule inhibitors, as well as antibody-based therapies such as immune checkpoint inhibitors or bispecific antibodies, are hence often first established as a continuous treatment until intolerable toxicity or disease progression. This treatment schedule applies to the first-in-class drugs such as venetoclax (BCL2i)[61] and ibrutinib (BTK inhibitor),[62] which showed long-term efficacy as continuous single-agents in high-risk chronic lymphocytic leukaemia. Capturing long-term treatment and (cumulative) adverse event trajectories is important in such continuous therapies. For example, 30% of 136 patients receiving the first-generation BTK inhibitor ibrutinib discontinue treatment due to adverse events.[62] In this setting, rigorous long-term adverse event reporting is necessary to uncover potential low-frequency, high-risk side-effects such as ventricular arrhythmias and associated deaths.[63] Duration of observation time is crucial as continuous treatments might accumulate adverse events over time, eventually surpassing the risk with time-limited treatments that might seem more toxic in the short term (figure 4). Therefore, longer follow-up[62] with granular adverse event reporting from continuous treatment trials is necessary to determine the true tolerability of a treatment. To this end, systematic collection of follow-up data from clinical trials in dedicated registries or long-term follow-up, low-intervention trials could be a solution. This data collection should be pragmatic to avoid undue burden and could be facilitated by (semi-automated) analyses from electronic health records.[64]

Efforts to reduce adverse events of small molecule inhibitors have been made in some cases by investigating more selective second-generation compounds in head-to-head comparisons versus first-generation

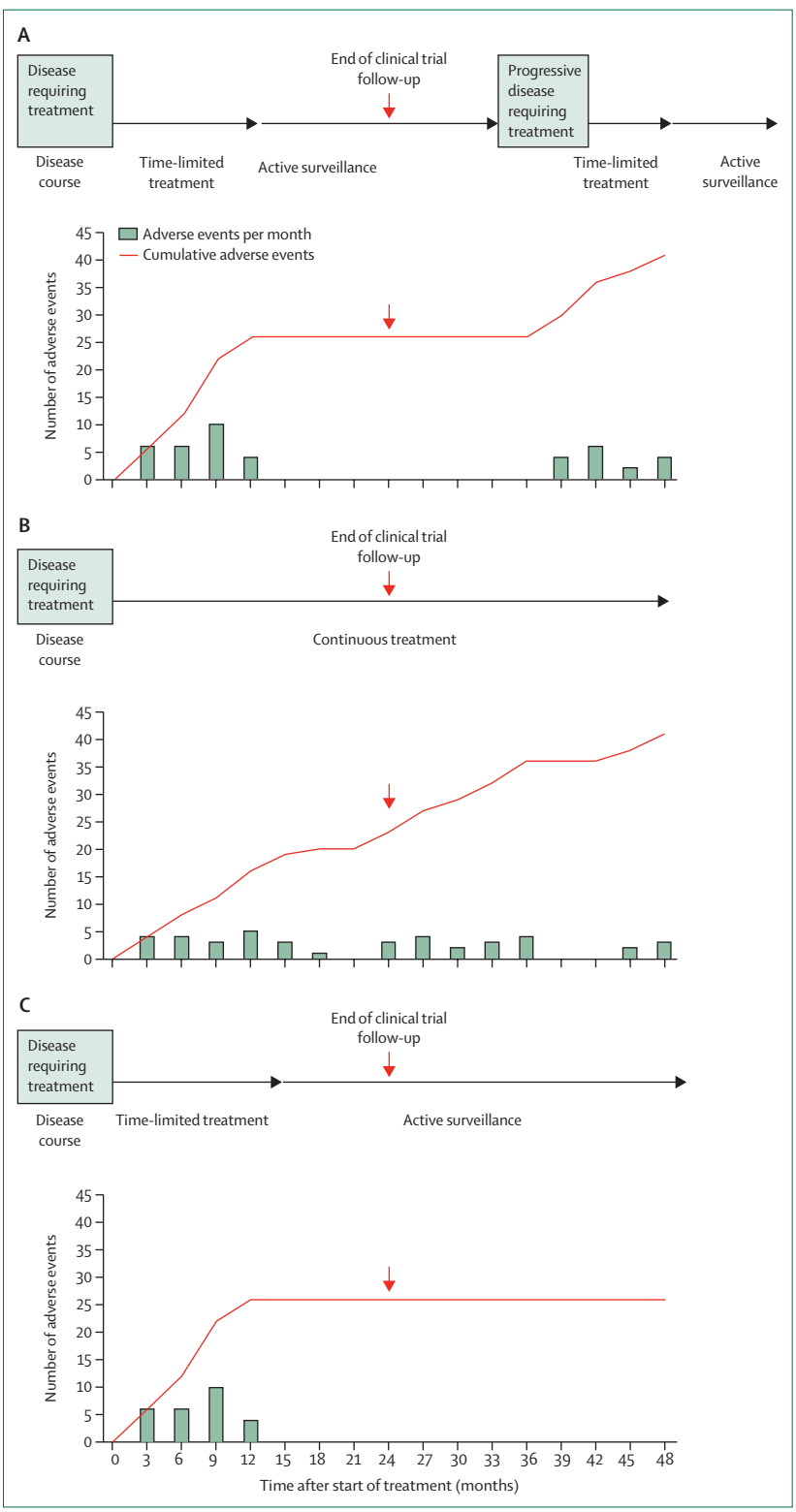

Figure 4: **A conceptual schema of adverse event trajectory and timing of study readouts in different treatment paradigms**
Schematic of treatment concepts in light of limited trial follow-up, resulting in similar results at trial readout for safety and efficacy with time-limited treatment with relapse (A), continuous treatment (B), and time-limited treatment without relapse (C).

drugs—an effort that is to be applauded. For BTKis, non-inferiority with an improved toxicity profile for acalabrutinib[65] and improved progression-free survival and toxicity profile for zanubrutinib[66] compared with ibrutinib were reported. Additional recent efforts combined targeted agents as time-limited treatments and, most importantly, tailored therapy duration based on best treatment response, for example, determined via measurable residual disease status. In the recently published FLAIR trial, such a strategy resulted in improved overall survival for treatment with ibrutinib–venetoclax versus fludarabine–cyclophosphamide and rituximab in chronic lymphocytic leukaemia.[67] Such efforts should be incorporated into trials with broader eligibility criteria, including clinically vulnerable patient groups at high risk of toxicity, such as patients who are older or who are frail.[68]

Lastly, dose-optimisation efforts might improve tolerability. During drug development, maximum-tolerated dose is usually sought to achieve maximum efficacy, but this approach derives from cytotoxic therapies where increased dose is generally associated with increased efficacy. Pharmacological studies have, however, shown—eg, in the case of ibrutinib—that much lower than approved doses can lead to similar target occupation,[69] as also discussed in the first paper of this Series. This observation is at least partially supported by real-world analyses showing similar, or even improved, outcomes in patients with reduced-dose ibrutinib treatment.[70] Efforts such as the FDA's Project Optimus, also described in the first and second papers in this Series, are aligned with these goals, and, if implemented, will be pivotal to pursuing the optimal target dose for patients with cancer.[71] Exemplified by the BCMA-targeted antibody–drug conjugate, belantamab mafodotin, which shows a dose-dependent and interval dependent incidence of ocular and haematological toxic effects,[72] pursuing minimum effective exposure might improve tolerability. Such efforts are ongoing (eg, NCT05932680) and could substantially reduce the considerable financial toxic effects associated with the high costs of novel therapeutics, thereby enabling easier access to these potentially lifesaving therapies.[73]

Thus, through efforts to optimise treatment duration, investigating time-limited approaches wherever feasible, and finessing dosing, aiming to identify a minimum effective dose rather than maximum-tolerated dose, harmful therapy exposure might and should be reduced. Only through adequate and complete reporting of adverse events with sufficient follow-up, ideally combined with PROs, are informed decisions on a best suitable therapeutic strategy possible.

Strategies to improve tolerability assessment with novel therapeutic approaches

Treatment paradigms for haematological malignancies are evolving. Comprehensive yet feasible assessment of tolerability is crucial to truly understand risks and benefit of promising therapies. Collaborative efforts are needed to overcome unmet needs. Currently, initial data are usually generated in clinical trials by industry sponsors who might exert gatekeeper roles with regard to assessment and reporting of toxicity and feasibility data. The involvement of industry sponsors might restrict the broader conduct of long-term analyses, post-market access studies, re-evaluation of optimal dosing, or collection and reporting of PROs. The current clinical trials model is not satisfactory and a mandate to share de-identified data is desirable to allow independent analyses (eg, within the YODA project). In the USA, such data sharing is mandated for government-funded trials, but this represents a small minority of trials in the modern era. Additionally, stringent implementation of the US FDA Project Optimus should be enforced to ensure every therapeutic is used at an optimal dose and schedule. Finally, a more effective infrastructure to allow capturing and merging data from the electronic health records for patients receiving therapies outside of trials should be created to allow longitudinal assessment of adverse events in representative groups of patients without undue burden on clinicians.

	Next steps	Long-term solutions
Current methods of adverse event capture do not facilitate the timely identification of unexpected acute and long-term toxic effects of novel therapies	Explore possibilities for real-time monitoring from data routinely available (eg, health-care records or wearable health devices); foster collaboration and revisit data-sharing frameworks between the different stakeholders in the clinical trials process; gather more details about infectious toxic effects and rare, but serious, toxic effects.	Mandate long-term follow-up of pivotal trials to capture long-term effects, including pooled data across individual trials for a given therapy; introduction of regulatory frameworks to leverage artificial intelligence and machine-learning technologies with the aim to reduce errors and burden associated with manual adverse event identification and reporting in early phase trials; encourage patient-reported outcome reports in trials.
Reporting and assessment of tolerability of novel therapeutic approaches are incomplete and currently scarce	Identify hurdles towards feasibility of unbiased reporting of toxic effects during and after treatment; explore opportunities to make safety data from pivotal trials publicly available for secondary analyses; generate and share post-approval safety data with real-world use, particularly in patient groups who are frequently excluded from trials.	Mandate the proper conduct and funding of independent post-market access studies; implementation of publicly accessible safety data repositories; increasing feasibility by defining core sets of expected adverse events in a setting with more streamlined and semi-automated and automated approaches for reporting.
Efforts to improve tolerability by optimising drug exposure are not widespread	Revisit early-phase trial concepts to identify minimum effective *vs* maximum-tolerated dose; prioritise time-limited treatments where feasible, especially in curative settings.	Support the development of measurable residual disease-guided and biomarker-guided treatments, including de-escalation strategies; prioritise innovative trial designs, ideally with early randomisation between different treatment concepts; ensure further dose-optimisation studies are conducted after initial market authorisation, including for combination approaches.

Refer to Figure 5 and other papers in this Series for more details.

Table: **Priority issues and challenges in the tolerability assessment of novel therapeutic approaches and potential steps to address them**

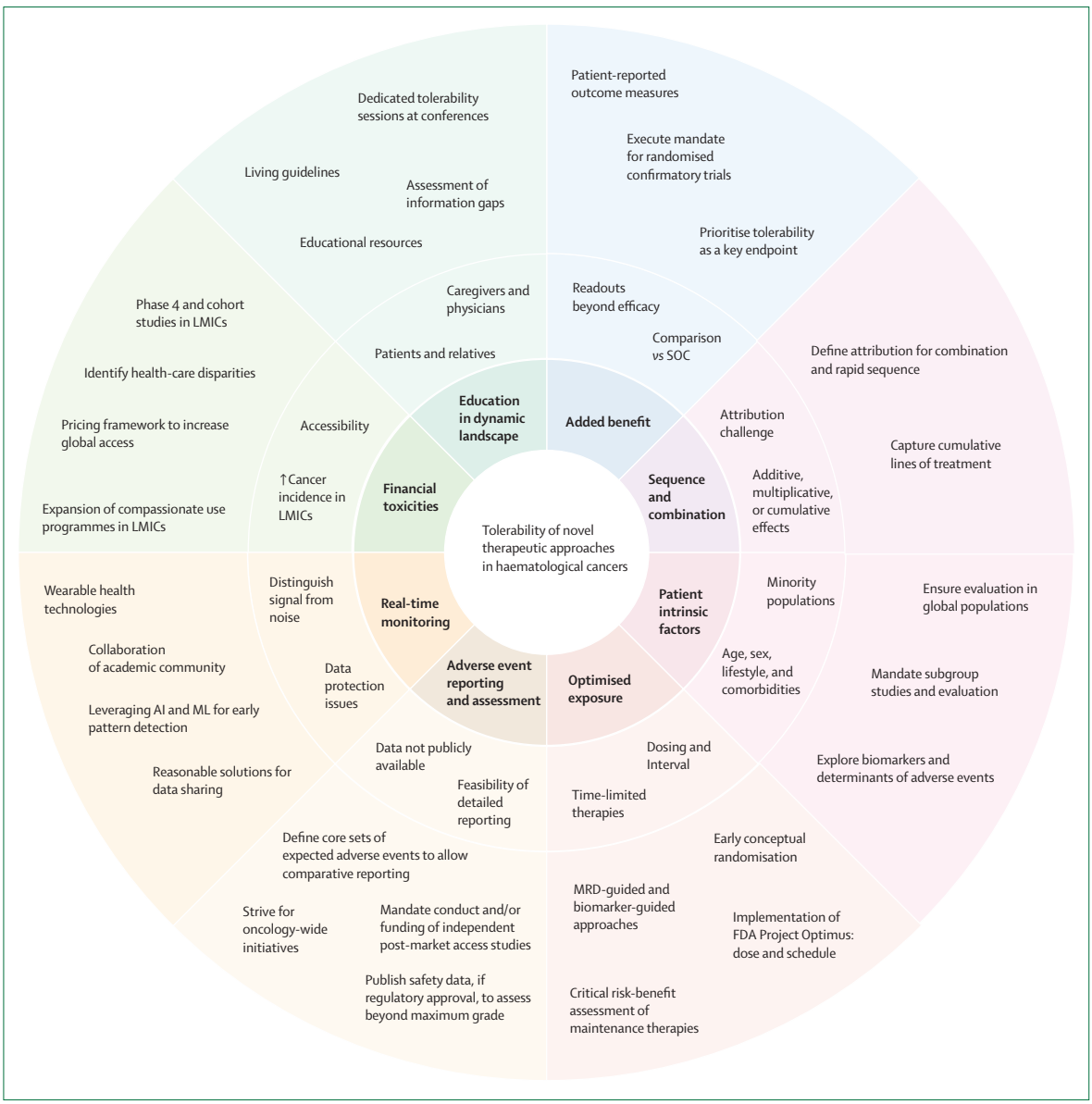

Figure 5: **Challenges, unmet needs, and future perspectives for tolerability assessment of novel therapies**
Schematic depiction of key issues (inner level), more detailed unmet needs (middle level), and potential approaches (outer level) for tolerability assessment of novel therapeutics. SOC=standard of care. LMICs=low-income and middle-income countries. AI=artificial intelligence. ML=machine learning. MRD=minimum residual disease.

The resulting mergeable, large, granular datasets (appendix p 1) would facilitate leveraging the striking performance and rapidly improving capabilities of machine-learning models, especially for pattern recognition. Such models are increasingly capable of leveraging various data sources and formats and, once established, semiautomated and automated analyses of data from routine clinical care such as laboratory test results, vital signs, and, potentially, wearable health devices could be conducted in real-time to identify unexpected adverse events. Such efforts depend on adequate handling and analysis of the resulting large multimodal datasets. Importantly, such approaches appear poised to assess adverse-event-associated clinical features for potential baseline or on-treatment risk assessment allowing early recognition of adverse events and pre-emptive intervention. In light of limited resources and ever-increasing regulatory hurdles for clinical trial conduct, this could be an important strategy to generate high-quality evidence with reduced administrative burden.

The toolbox to successfully treat our patients is ever expanding. This increased range of therapeutic options poses a considerable challenge to providing education on side-effect profiles to patients, relatives, and their caregivers. To enable treating haemato-oncologists to

Search strategy and selection criteria

References addressing the key issues and concepts outlined in this Series paper were identified by the international author panel through focused searches in PubMed and Abstract Books of the major haematology conferences. No systematic search or review of the literature was conducted.

live up to this important responsibility, concise, accurate, up-to-date, and actionable information resources for emerging therapeutics should be developed. Industry sponsors should ideally fund the required infrastructure, which should be under leadership of the academic and regulatory community and involve key stakeholders, including patient advocates. Depending on the context, this could include educational resources on class-specific (eg, immune-related adverse events with immune checkpoint inhibitors), target-specific (eg, ocular toxicities with BCMA antibody–drug conjugates), or disease-specific (eg, management of T-cell activating therapies in aggressive B-cell non-Hodgkin lymphoma) topics. The effects of age, sex, ethnicity, lifestyle factors, and social determinants on health should be considered. Under-representation of many patient groups in pivotal clinical trials severely hampers our understanding of toxicities; for example, in children, those who are older or frail, and ethnic minorities. Such patients might have very different tolerability due to variations in immune landscape, metabolism, comedication, or comorbidities. It will be important to investigate novel therapeutic strategies in studies that include these patient groups.

We aim to provide a schematic overview of these and additional issues in summary of this call to action in the table and figure 5. Hereto, the insightful accompanying Comment by Lingaraj Nayak and colleagues is an important reminder to address financial toxic effects and inequality in access to novel therapeutics, which poses one of the biggest hurdles to achieving maximum benefits on a global scale.[74] Trial sponsors, investigators, regulators, medical journal editors and reviewers, and clinicians will all need to work together to ensure the robust and rapid reporting, assessment, and mitigation of toxicities to novel therapies to ensure the best outcomes for all patients.

Contributors

PJB and GT conceived the outline of the manuscript as lead authors. PJB, ERSC, GI, and FS drafted the first version of the text and figures. All authors contributed to the outline of the manuscript, search and selection of the literature and critically reviewed, edited, and approved the final version of the manuscript.

Declaration of interests

PJB is an advisor or consultant for Hexal, Merck Sharp & Dohme (MSD), Need, Stemline, and Takeda; holds stock options in Need, has received honoraria from AstraZeneca, BeiGene, Bristol-Myers Squibb (BMS)–Celgene, Eli Lilly, MSD, Need, Stemline, and Takeda; and reports research funding from BeiGene (paid to institution), BMS (institution), MSD (institution), and Takeda (paid to institution). GI has received honoraria or travel support from Abbvie, AstraZeneca, Autolus, BMS, Kite–Gilead, Miltenyi, Novartis, and Sandoz. FS has received honoraria or travel support from AstraZeneca, Eli Lilly, and research support from AstraZeneca (paid to institution). MMH served as a consultant for Sobi; and receives research funding from Incyte Corporation and Mesoblast. AK has received honoraria from Kite–Gilead for data safety monitoring board activities. MVM has received honoraria for lectures of participation in advisory boards from Johnson & Johnson, BMS, Amgen, Pfizer, Sanofi, GlaxoSmithKline (GSK), Kite, and Stemline. MM has received research grants from Janssen, Novartis, and Sanofi; and honoraria for consulting or lectures from Adaptive Biotechnologies, Amgen, Astellas, BMS, GSK, Janssen, Jazz, Novartis, Pfizer, Sanofi, Stemline, and Takeda. YS has served as an advisor for AbbVie, AstraZeneca, BeiGene, and Roche; received honoraria from AstraZeneca, BeiGene, and Roche; and reports travel support from BeiGene and Roche. JRW is a consultant to Ansun, Cidara, Celgene, F2G, Orca, Karius, Pearl Diagnostics, and Takeda. GT has been a consultant for Novartis (2023) and Seagen (2022). All other authors declare no competing interests.

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