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Review

The future of research in hematology: Integration of conventional studies with real-world data and artificial intelligence

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ABSTRACT

Most national health-care systems approve new drugs based on data of safety and efficacy from large randomized clinical trials (RCTs). Strict selection biases and study-entry criteria of subjects included in RCTs often do not reflect those of the population where a therapy is intended to be used. Compliance to treatment in RCTs also differs considerably from real world settings and the relatively small size of most RCTs make them unlikely to detect rare but important safety signals. These and other considerations may explain the gap between evidence generated in RCTs and translating conclusions to health-care policies in the real world. Real-world evidence (RWE) derived from real-world data (RWD) is receiving increasing attention from scientists, clinicians, and health-care policy decision-makers - especially when it is processed by artificial intelligence (AI). We describe the potential of using RWD and AI in Hematology to support research and health-care decisions.

1. Introduction

In most resource rich countries health care systems approve drugs and interventions based on evidence of safety and efficacy. Although data from large randomized clinical trials (RCTs) are considered the highest level of evidence, there are sometimes contradictory conclusions from seemingly similar RCTs [1]. Moreover, results of RCTs often do not apply to many persons with a disease because of subject selection biases and study-eligibility criteria [1]. Furthermore, even when a RCT shows a convincing benefit of an intervention, this benefit is often not equally distributed among the intervention recipients. Sometimes even when there is an aggregate benefit some subjects are harmed by the intervention [2–4]. These limitations impose gaps between evidence from RCTs, evidence from real-world data (RWD) and health care policies. This gap is particularly critical for haematological cancers where interventions are complex, costly and with substantial potential of adverse events.

Evidence generated by analysing RWD is receiving increasing attention from scientists, clinicians, and health care policy decision-makers. Analyses of RWD also allow drug companies and regulators evaluate the safety and efficacy of drugs post-approval. Artificial intelligence (AI) has the potential to implement these analyses. In this review, we discuss strengths, weaknesses, and the potential of real-world evidence (RWE) in clinical decision-making in hematology.

2. Real-world data (RWD) and real-world evidence (RWE)

2.1. Why should we consider data outside of RCTs?

RCTs are considered the highest level of evidence for safety and efficacy. Randomization of sufficient numbers of subjects maximizes the likelihood differences in outcome results from an intervention rather than selection biases and known and unknown confounders and covariates [5]. However, RCTs have subject selection and study-

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eligibility criteria which prevent most people with the disease being studied from participating [6]. Moreover, subjects receive the intervention in highly controlled setting unlike those in clinical practice. Subjects must give written informed consent for enrolment. Considerable data indicate compliance in RCTs far exceeds that observed in settings outside of clinical trials [7]. Participation in a RCT is generally considered to be motivated by altruism as the subjects may receive a better or worse intervention. This motivation differs from those of people receiving the same intervention in a non-clinical trial setting. RCTs are typically brief and do not include monitoring of subsequent interventions. Consequently, almost all RCTs devolve into observational databases with many known and unknown confounders. Because of these and other considerations, conclusions from RCTs have limited generalizability for clinical practice [8–11].

A new wave of medical innovation is likely to play a key role in the future of health care systems. About 7000 drugs are in development including 1813 anti-cancer drugs [12]. Regulatory agencies operate under the dual tension of providing rapid access to new therapies but ensuring safety and efficacy [13]. Innovative marketing authorization pathways such as conditional approval and fast-track/accelerated approvals have been developed to accelerate the traditionally long, cumbersome drug approval process [14–16]. Between 1992 and 2017, the US Food and Drug Administration (FDA) used single-arm trials and surrogate endpoints for accelerated approval of 67 anti-cancer drugs [17]. However, rapid authorization should be given only if the benefit of immediate availability of a drug outweighs the risk of not having comprehensive data to critically evaluate safety and efficacy [18,19]. Moreover, few drugs receiving accelerated approval are subsequently tested for safety and efficacy in FDA mandated post-approval trials leading FDA and other regulatory agencies to refer to these as *dangling* [20,21]. For example, some immune therapy drugs were recently withdrawn after having had accelerated approval [22]. This results in a loss of public trust in the decision process of regulatory authorities [23].

In a clinical trial setting such as a phase-1 trial, few subjects receiving investigational therapies benefit whereas all subjects are exposed to potential adverse events [24–26]. Consequently, safety and efficacy of an intervention in a trial participant is uncertain and depends on many co-variates such as type and stage of disease, pharmacokinetic and -dynamics, therapy setting, demographics, socio-economics and others.

To improve health outcomes at sustainable costs it is necessary to select people most likely to benefit [27,28]. Survival of people with cancer has improved over the last 30 years paralleling substantially increased drug costs *per* quality adjusted life year (QALY) [29–32]. This explains the increasing attention to value-based health care defined by relevant outcomes from medical, recipient and payor viewpoints [33]. The aim is maximizing value: reaching the best outcome at the lowest cost [34]. The challenge is defining and quantifying outcomes and costs [35].

2.2. Are there alternative or better study designs than RCTs?

There are possible alternatives to RCTs to determine safety and efficacy in the real world. Pragmatic clinical trials (PCTs) have more liberal inclusion criteria resembling those used in clinical practice [36,37]. However, methodological, ethical and legal standards and costs are as high as conventional RCTs [38]. Therefore, less expensive, and alternative study-designs are needed for generating RWE [39,40].

In prospective observational studies (POSs) group assignment is neither randomized nor specified. Participants are enrolled on-study before receiving an intervention. PCTs and POSs share the same statistical strength of generalizability and external validity. However, these studies require time, money and resources not always available. In POSs, the lack of randomization with potential biases and confounding factors limits internal validity.

In a retrospective observational study (ROS) the intervention and outcome occur before starting the analysis. The challenge is recognizing component(s) explaining clinical outcomes and health care costs in the present using heterogeneous health care pathways experienced in the past. Thanks to diverse input data, ROSs could answer to questions on epidemiology, unmet medical needs, health care pathways, socio-economic and clinical co-variates of participants, safety, efficacy, and cost-effectiveness profiles experienced in the real world. This becomes of special interest in rare haematological cancers. However, selection biases and confounding are major concerns because of unrecognized baseline differences. As for the presence of confounding variables, we need to take into account the Simpson's paradox that refers to the reversal of the direction of an association when data from two or more groups are combined to form a single group.

2.3. Do we have enough data to properly investigate drugs in the real world?

According to FDA RWD related to patient health status and/or delivery of healthcare are routinely collected. Sources for generating RWE are the electronic health records, claims and billing activities, disease or drugs registries, patient-generated data including those stored in home-use settings or in mobile devices. However, there are several constraints on informing clinical practice using RWD. First, subject-level data is needed (i.e., data of each person should be available). Second, population-based data archive should be done (i.e., the target population from which the disease cases of interest originate should be known). Third, the population sample should be large, especially when dealing with new treatments, poorly represented phenotypes/genotypes, and rare diseases. A possible solution to these requirements is using of Electronic Healthcare Utilization (EHU) data created to pay providers of health care services [41]. These EHU data have several advantages: (1) The electronic format database can be obtained without great cost, over long intervals and quickly; (2) A unique anonymized identifier assigned to each person could be linked to datasets to track healthcare given over time; (3) Informed consent is not usually required for collecting and storing EHU data [42] and (4) The data reflect clinical practice especially in the context of a national health care system [7].

The real barrier to using EHU data is that data are collected for health care management and not for research. Therefore, important biological, clinical and therapy information may not be captured or, if captured, may not be in a useable, compatible form or a combination. Consequently, data sharing processes are needed to capture additional information and outcomes [43]. Examples are cancer registries, health data from referring centres, smart home apps and wearable digital medical devices. These are the new frontiers of research in the real world setting.

There are limitations when analysing EHU as RWD. First, one needs to collect population-based data to avoid or limit selection biases and confounders. Second, generalizability of RWD is not always possible. Results obtained in one population may not apply to another. Third, data sharing requires universal or at least inter-operable technical standards [44]. Finally, from an ethical and legal viewpoint, data protection legislation is critical [45]. It is important to regulate personal data processing and sharing whilst pursuing the public interest to avoid the conflict between personal and research freedom [45]. Technological solutions are now available to safeguard subjects' rights and respect General Data Protection Regulations [46]. Systems based on Data Sharing Federation (DSF) are among the most promising [47]. Data are stored at partner sites and can be viewed by mutual agreement by researchers only after guarantees of subject privacy and data confidentiality protections [47].

2.4. Can credible evidence be generated from real world observations?

It is unlikely a RWD repository or DSF-based system could instantaneously increase our knowledge of the real world. The challenge is to interrogate these data and generate useful and credible evidence. The latter refers not only to capture big data (large volumes of structured and

unstructured data from several sources) but the ability to design appropriate studies, use correct analyses and scientific methods and inform healthcare decision-making [44,48,49]. Explanatory (hypothesis testing) and exploratory studies can be done with RWD. Explanatory studies typically aim at evaluating pre-specified effects focusing on their magnitude (effect size). They share with RCTs an a priori hypothesis to test. Exploratory investigations represent a first step in learning about possible effects of interventions. A typical example is a study to determine which subjects in a population are most likely to benefit from an intervention.

Because both types of investigations can provide credible RWE, we emphasize the need for pre-defined shared good practice rules in terms of study-designs, data analytics and results reporting. The latter should be made explicit in a protocol ideally approved by an independent Expert Committee. Exploratory studies cannot not have the same pre-planned structure compared with explanatory ones.

In summary, the potential of real world studies is to interrogate appropriateness, impact, and costs of health care practices in the real world (explanatory studies), define disease outcome, and profile patients according to their likelihood of benefit (exploratory investigations). Consequently, the major ethical constraint is generating credible RWE. This implies good clinical research practice rules and evaluation of the risk of systematic uncertainty.

3. Artificial intelligence and RWE

Increasing volumes of RWD have been produced following the development of specialist devices and sophisticated data collection techniques. Together with technological advancements including computing power and storage, there is an opportunity for powerful AI approaches to be applied to these data to process and provide valuable insights for patient benefit. In the context of drug development, the application of AI to RWD and subsequent generation of RWE has huge potential with examples including analysis of patient treatment pathways, risk of disease development for patients, tracking patient behaviour and adherence [50]. We can consider two aspects of AI being particularly important for RWD/RWE: natural language processing (NLP) and machine learning (ML). NLP is an AI tool attributable to the ability of a computer program to understand the human language and automatically extract contextual meaning [51]. NLP offers an automated way to effectively process unstructured text, which is particularly useful given that large amounts of RWD are unstructured yet potentially rich in information (i.e., in the form of clinician notes, patient diary entries or even social media). Processing the unstructured text in this way can be useful for many different applications, including preparing the data for an algorithm to predict an outcome or result [52].

ML is a computer algorithm that can build a mathematical model based on a set of training data to make predictions on unseen data (test data) without being explicitly programmed [53]. Over the last 15–20 years, ML has gradually replaced traditional statistical inference as the tool of choice for learning complex relationships in data. The key advantage of ML is the capability to operate on large numbers of engineered predictive features in datasets including outliers, noise, and collinearities, without concerns on stability and reliability of traditional statistical modelling [49,54].

There are different categories of ML including supervised (where the desired output is known) and unsupervised (where the desired output is not known) and different types of models within these categories [55,56]. The category and model employed in an ML approach are dependent upon the problem, data, and constraints. One of the most intriguing and potentially game changing examples of ML is its application to the area of predictive and prescriptive analytics. The latter are now used to identify patients most likely to benefit from certain treatments, those likely to be adherent to therapy, or even those likely to develop an adverse event. Traditionally, risk analytics have been performed using standard statistical techniques, such as stepwise logistic regression. In these approaches, characteristics or risks are identified and added into models to determine their impact on the model performance. While predictive analytics can be generated using traditional statistical approaches, ML enables models to be generated to include thousands of variables and millions of data points. The result is usually more highly performant models as well as the ability to uncover more data relationships of importance, which might not have been so prior to the analysis [57]. Table 1 summarizes strengths and weaknesses of the different type of studies, RWD and AI.

4. Future use of RWE in haematological cancers

4.1. Closing the gap between results from clinical trials and the real world

New innovative drugs or procedures are often expensive and their use must be monitored. For example, the immediate direct drug cost of chimeric antigen receptor (CAR)-T-cell therapy is $370–480.000 USD per recipient. However, this estimate fails to consider therapy of complications such as cytokine release syndrome which increases costs to >1 million USD. Nor does it consider costs incurred over a lifetime which can be captured by RWD (reviewed in [58–60]). Most trials of safety and efficacy of CAR-T-cell therapy are single-arm, open-label and unblinded with no comparator cohort and brief follow-up. Consequently, the main task for RWE in this setting is analysing safety and efficacy in a larger, more diverse population with longer follow-up. In the real world, and unlike many clinical trials participants, persons most likely to receive and/or benefit from CAR-T cell therapy are older with substantial comorbidities and could potentially be at increased risk to develop therapy-related adverse events [61].

Recently, plenty of RWD on CAR-T cells for relapsed/refractory large B cell lymphoma has been published. With respect to registration trials, safety profile seems comparable. As for efficacy, only some RW studies reported slightly lower responses, probably due to a more advanced patients' population or to the exclusion of subjects who did not indeed receive CAR-T cells after collection [62–65]. Besides, preliminary report of a real world prospective observational study conducted by the Italian Society of Hematology has confirmed feasibility and efficacy of CAR-T cells in highly pretreated aggressive B lymphomas, but also showed cytopenias as an emerging adverse event in the RW setting [66]. Data from RWD processed by AI could identify persons in which CAR-T-cell therapy is most appropriate and indicate lifetime cost.

In some settings, RWE has been crucial to support the findings of conventional studies.

Ruxolitinib (RUX) is the first JAK inhibitor approved for the treatment of myelofibrosis. Efficacy of RUX in terms of clinical improvement and outcome has been extensively described in many clinical trials [67,68]. The survival benefit of RUX has recently been confirmed by preliminary data on a European registry [69]. Also, incidence of RUX discontinuation seems comparable between trials and RWD [67,68,70–72]. Excluding the well-defined events of death and blast phase (BP) transformation, reasons for stopping RUX appear to have slightly different rates in RW studies. This probably reflects ununiform RUX dosing strategies or the absence of agreed-upon criteria for RUX refractoriness, intolerance, or relapse [68,70,71]. Besides, some differences could be found as for survival estimates after RUX discontinuation. In the RW setting, BP evolution did have a detrimental impact on outcome, while in a phase 1/2 study the reason for RUX discontinuation was not associated with survival. This is probably due to a larger patient population or a lower accessibility to investigational salvage therapies/allogenic transplant in the RW setting [70,73].

For other haematological therapies, the discordance between efficacy in the setting of clinical trials compared with real world is more evident. This highlights the importance of conducting real world analyses of cancer treatment outcomes, with a focus also on the real world toxicities which have a strong impact in patients' quality of life and prognosis.

Consider acute myeloid leukemia (AML) where about one-half of people >65 years in the US receive no therapy within 4 months of diagnosis and about one-third are >75 years [74,75]. These older persons are frequently ineligible to participate in clinical trials. Consequently, data from the few phase-2 and RCTs published in this age cohort of interventions such as hypo-methylating drugs with or without venetoclax or targeted therapies such as enasideinib or ivosidenib are unlikely representative of what would be achieved with this intervention in a real world setting [76–81]. For example, two studies reported much lower response rates and worse survival with venetoclax and azacytidine in real world recipients compared with seemingly comparable persons in RCTs [82,83].

Other examples are studies on survival in higher-risk patients affected by myelodysplastic syndromes (MDS) treated with hypomethylating agents. A systematic review of various label multicenter phase III RCTs [84–87] comparing hypomethylating therapy with different conventional care regimen, and a systematic review reports a significantly higher response rata and survival advantage compared to other conventional care regimens, with a median overall survival of 24 months [88]. However, real world analyses in higher-risk MDS have failed to demonstrate the survival benefit with hypomethylating agents, with a reported median OS almost half than what reported in the RCT, ranging from 11.6 months to 16.9 months [89–92], reflecting the differences in age, comorbidities, toxicity and infectious complications in the real world setting.

4.2. Disease epidemiology

RWE could properly provide information on disease epidemiology. For example, Orphanet provides important estimates of incidence and prevalence of so-called rare diseases such as Gaucher disease and severe combined immune deficiency (SCID) compared with other data sources. RWD and AI can help to identify mimicking conditions in the population. The epidemiology of SARS-CoV-2-infection in persons with haematological cancers was estimated by National RWD collections and the high rate of mortality confirmed by multi-national registries and meta-analyses [93–99].

4.3. Rare adverse events

Finally, structured, or unstructured RWD can might enable us to identify rare adverse events. For example, consider persons with primary myelofibrosis receiving RUX [100–103]. Several case reports and two observational datasets reported an increased risk of non-Hodgkin lymphomas in persons receiving RUX [104,105]. However, these data are potentially compromised by selective reporting and publication biases. In contrast, data from RWE reported no increased risk [72]. This is one of paradigmatic example of the value of RWE for assessing rare long-term adverse events associated with new therapies of haematologic cancers [106]. In Table 1, we have summarized the strenghts and the weaknesses of the different types of studies, of RWD and AI.

5. Conclusions and future directions

We review the potential utility of RWE to provide high quality evidence of safety and efficacy and a basis for clinical decision-making in haematological cancers. We emphasize the need of RWE for cost-effectiveness and -utility analyses and for closing the gap between estimates of safety and efficacy from data derived from clinical trials versus RWE. We also emphasize the importance of using RWE to understand disease epidemiology and monitor rare adverse events. We highlight the need for pre-defined rules on study-designs and data analytics for a reliable real world study. Although data from RWE cannot replace RCTs it is needed to support effective and efficient health care decisions. In the future the technology advancements of AI will offer researchers the ability to increase meaningful RWE output, decrease

Table 1
Strengths and weaknesses of the different type of studies, real-world data and artificial intelligence.

Type of study	Strengths	Weaknesses
Randomized Controlled Trial (RCT)	• High internal validity • Randomization • Proven and stringent study design • Indispensable for the authorization of new medications [38]	• Low external validity and generalizability • Stringent selection of the patients, socio-demographic biases • Inadequate determination of long-term toxicity • Frequent use of surrogate parameters as primary endpoints • Time and resource-intensive [38]
Pragmatic Clinical Trials (PCT)	• High external validity and generalizability • Inclusion of comorbidities: better representation of the real patient-population • Flexibility in how to apply the intervention • Increased access to experimental therapies • High social value (by telling us if an intervention is likely to be effective in routine clinical practice) [36,37]	• Low internal validity • Logistical challenges as ethical barrier, genuinely unselected patient access, recruitment of investigators [36,37]
Prospective Observational Studies (POS)	• High external validity and generalizability • Accuracy of data collection with regards to exposures, confounders and endpoints • Possibility to study multiple exposures and multiple outcomes • Possibility of hypothesis generation [107]	• Low internal validity • Risk of bias and confounding factors (loss-to-follow-up) • Not suitable to establish causal effects • Expensive and time-consuming [107]
Retrospective Observational Study (ROS)	• Possibility to study rare diseases and exposures • Possibility of hypothesis generation • Time and cost efficient thanks to already existing data [108]	• Risk of selection bias and confounding factors (unrecognized baseline differences, missing data) • Non-adherence to an endpoint to be investigated for cause • Not suitable to establish causal effects [108]
Real Word Data (RWD)	• High external validity and generalizability • Possibility of long-term surveillance • Detection of less frequent side effects • Prediction model or high-risk group selection • Time and resource-efficient • Set a foundation on artificial intelligence [109]	• Low internal validity • Risk of inadequate study design and biased data • Lack of privacy and confidentiality data • Need of experienced experts for the analysis of the massive amount of data • Need of standardized research protocol [109]
Artificial Intelligence (AI)	• Wide field of application • Possibility to do explanatory studies and exploratory investigations • Strategy to use the quantity and complexity of the RW data • Consistent reference standard in pathology that could serve either to support diagnoses or to prompt review by another individual	• Need of extensive databases before providing useful results • Risk of bias from low data quality • Need of models providing insight into the logic behind the association between predictors and outcomes and into the clinical applicability [110,111]

(*continued on next page*)

Table 1 (*continued*)

Type of study	Strengths	Weaknesses
	• Potential to provide more refined, personalized prognoses • Genomics data analysis • Selection of the patients most likely to benefit from an intervention can lower costs and increase the likelihood of finding use for new therapies [110,111]	

time to insights and make the most currently available data sources.

Practice points

- RWD have many fields of application and advantages (e.g., high generalizability), but clear guidelines on minimal technical standards should be generated to reduce the risk of selection biases and confounders
- RWE represents the best way to close the gap between research and clinical practice, validating RCT results but also investigating appropriateness, patients' selection for new therapies, impact and costs of health care practices in the real world setting.
- AI gives us the strategy to use the huge amount and complexity of data coming from real word but also from the new technology investigating genetic signature, transcriptome and proteomics, in order to refine risk disease stratification and prognosis and to discover new therapeutic targets for haematologic cancers.

Research agenda

- To create an international data sharing of easily available, extensive, and reliable RWD of haematologic cancer patients.
- To use AI to process RWD with the aim to have a personalized patient's prognostication and choice of therapy.
- To use AI to interpret comprehensive -omics datasets from preclinical research and to develop algorithms delivering smart data processing, analysis, and outcomes of the patients with haematologic cancer.

Declaration of Competing Interest

RPG is a consultant to BeiGene Ltd., Fusion Pharma LLC, La Jolla NanoMedical Inc., Mingsight Parmaceuticals Inc. and CStone Pharmaceuticals; advisor to Antegene Biotech LLC, Medical Director, FFF Enterprises Inc.; partner, AZAC Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd.: F.P. served in Speaker Bureau for Novartis, Celgene, BMS, Janssen, Abbvie and received research grants from BMS. G.C. took part in a variety of projects that were funded by pharmaceutical companies (i.e. Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as a member of the advisory board to Roche.

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