Expert Opinion on Drug Safety

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Pharmacovigilance of anti-cancer medicines: opportunities and challenges

Diana Crestan , Marta Paulina Trojniak , Sara Francescon , Giulia Fornasier & Paolo Baldo

To cite this article: Diana Crestan , Marta Paulina Trojniak , Sara Francescon , Giulia Fornasier & Paolo Baldo (2020) Pharmacovigilance of anti-cancer medicines: opportunities and challenges, Expert Opinion on Drug Safety, 19:7, 849-860, DOI: 10.1080/14740338.2020.1772751

To link to this article: https://doi.org/10.1080/14740338.2020.1772751

Published online: 18 Jun 2020.

EXPERT OPINION ON DRUG SAFETY
2020, VOL. 19, NO. 7, 849–859
https://doi.org/10.1080/14740338.2020.1772751

Taylor & Francis
Taylor & Francis Group

REVIEW

Pharmacovigilance of anti-cancer medicines: opportunities and challenges

Diana Crestan [a], Marta Paulina Trojniak[b], Sara Francescon [a,c], Giulia Fornasier [b] and Paolo Baldo [a]

[a]Pharmacy Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy; [b]Hospital Pharmacy Unit, Institute for Maternal and Child Health "IRCCS Burlo Garofolo", Trieste, Italy; [c]Department of Hospital Pharmacy, Azienda Sanitaria Universitaria Friuli Centrale, ASUFC, Udine, Italy

ABSTRACT

Introduction: The foundations of pharmacovigilance are the monitoring of drug safety in real-world medicine, and identification of new adverse effects, unknown at the time of market approval. Cancer patients are prone to adverse drug reactions due to the complexity of the neoplastic disease and its treatment. Pharmacovigilance of anti-cancer medicines is further complicated because patients have comorbidities, as for elderly patients. It is even more challenging when complete safety and risk data for a drug are lacking, as may occur for new molecules or when it comes to drugs for children.

Areas covered: This article introduces the field of pharmacovigilance of anti-cancer drugs, describing the various layers of complexity that make the recognition of adverse drug events in oncology particularly problematic, including the type of medicines, the phenomenon of underreporting and polypharmacy. Finally, it reviews new digital tools to help pharmacovigilance activities in oncology.

Expert opinion: The authors outline some crucial challenges and opportunities that can be useful for pharmacovigilance to keep up with the times and follow the current technological and scientific progress. In addition to the evaluations made by researchers, it will, of course, be necessary to have an equality important concrete response from the institutions and regulatory bodies.

ARTICLE HISTORY
Received 9 October 2019
Accepted 19 May 2020

KEYWORDS
Pharmacovigilance; adverse drug reaction; clinical oncology; patient reported outcomes; under-reporting

1. Introduction

Pharmacovigilance (PV), defined by the World Health Organization (WHO) as the 'science and activities related to the detection, evaluation, understanding and prevention of adverse effects or any other drug-related problem' [1], aims to improve patient safety and quality of life. There are several objectives of pharmacovigilance, starting with the collection and management of safety data, to promote the safe and effective use of medicines.

Pharmacovigilance also aims to provide information on drug safety to health professionals and patients, and it contributes to updating drug labels. Finally, it is active in risk management, risk minimization and the prevention of adverse effects and other drug-related problems. As defined by WHO [2], an adverse event (AE) is 'any untoward medical occurrence that may be present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment'. When there is a causal relationship with the treatment, an AE is classified as an adverse drug reaction (ADR), 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'.

The collection and reporting of AEs is a process that starts from the drug development phase and proceeds continuously throughout the life cycle of the drug, and it aims to assess the benefits-to-toxicity ratios (in other words, the safety and efficacy) of all medicines [1]. Drug safety reports may lead to actions such as the introduction of a warning in the drug label, stricter monitoring or even drug withdrawal for safety reasons [3]. Sources of drug safety data may be direct (i.e. spontaneous reports from patients or health professionals that are transmitted to the marketing authorization holder or to a health authority) or indirect (i.e. information derived from sources other than spontaneous reports, such as case reports, clinical trials, registries, and social media). Drug safety data is also collected by healthcare systems (e.g. prescriptions).

Reports of ADRs must accurately describe the case and be meaningful to health professionals worldwide. To guide the standardized reporting of ADRs in oncology, the US National Cancer Institute established the Common Terminological Criteria for Adverse Events (CTCAE) [4]. In CTCAE, the severity of an AE is ranked from 1 to 5. The Medical Dictionary for Regulatory Activities (MedDRA) [5], which guides the clinical-pathological classification of AEs, is another tool that supports accurate ADR reporting. Recently, the US National Cancer Institute released a tool to facilitate patient reporting of symptomatic toxicity during cancer clinical trials, as a companion to CTCAE. This tool is called PRO-CTCAE (Patient-reported outcomes CTCAE) [6].

In this article, we critically evaluate the main issues in the pharmacovigilance of cancer medicines. We discuss areas for improvement and prospects for the future, in order to understand the challenges of modern pharmacovigilance in oncology.

1.1. Organization of pharmacovigilance in Europe

In the European Union (EU), pharmacovigilance legislation aims to protect public health through: (1) the collection of

CONTACT Paolo Baldo pbaldo@cro.it; ims@cro.it Pharmacy Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano 33081, Italy

Article highlights

- Pharmacovigilance still involves many challenges in oncology.
- Implementation of international electronic reporting systems means not that also clinical management of ADRs is well-known and standardized.
- Underreporting of adverse drug reactions in oncology is a major problem.
- Safety of newer targeted cancer drugs must be strictly monitored, to implement individual toxicologic profiles and expand knowledge.
- Modern pharmacovigilance in oncology must proceed in the direction of risk prediction and personalization of ADR management.

This box summarizes key points contained in the article.

high-quality data on drugs and their safety; (2) the rapid and robust assessment of issues related to drug safety; and (3) the encouragement of patients to report ADRs and to participate in drug safety activities, thereby facilitating the identification of new signals of risk for patients taking drugs [7]. An early step in the development of European pharmacovigilance was the 1968 implementation of the Programme for International Drug Monitoring [1]. 1992 saw the founding of the European Society of Pharmacovigilance, now called the International Society of Pharmacovigilance [8]. The European Medicines Agency (EMA) was established in 1995. EudraVigilance, a system for managing information about suspected ADRs to medicines authorized in the European economic area, was created in 2001 [9].

European pharmacovigilance legislation (directives and regulations) aims to facilitate the management of medicinal product safety issues, increasing the possibility of identifying new signals of potential harm to the general population. For example, Directive 2010/84/EU defined an ADR as a 'noxious and unintended effect resulting from the use of a medicinal product' [10]. This definition includes reactions occurring as the result of error, misuse or abuse, including the off-label use of drugs [11]. Directive 2010/84/EU recommends that individual EU countries take steps to encourage citizens to report ADRs. The Pharmacovigilance Risk Assessment Committee (PRAC) in EMA, set up following Directive 2001/83/EC and Regulation 726/2006, authorized the possibility of imposing additional monitoring for specific molecules, including post-authorization safety and efficacy studies [12].

2. Pharmacovigilance in oncology: a matter of complexity

The rationale behind our intent to produce a review of PV in oncology lies in the particular aspects of this clinical context, namely the type of disease and the therapeutic and pharmacological treatments. Clinical research makes new therapeutic treatments available continuously; however, as we know, cancer still faces many difficult and unknown challenges. A unique toxicity profile is also expected from the new drugs, making treatment more tolerable while facilitating the management of symptoms.

However, even if with different outcomes, not even the most novel targeted therapies or biotherapies are free from side effects that are often relevant, and these can be massively underestimated or underreported by health professionals. The increase in life expectancy contributes to making elderly patients prevalent in the oncologic population, with probable comorbidities and physiological dysfunctions, such as hypertension, heart failure, renal or hepatic dysfunctions [13]. Therefore, clinical oncology becomes an area in which, more and more, the complexity of individuals adds up to very complex therapeutic and pharmacological treatments, all potentially responsible for toxicity and risks of adverse reactions [14]. The scientific and regulatory criteria that, starting from the history of Thalidomide to today, have allowed in these decades the evolution of the Pharmacovigilance discipline, providing the market safer drugs and helping patients to manage severe side effects better, they are applied in the same way to clinical practice in general medicine and also in oncology. Still, the oncological field, precisely because of the intrinsic characteristics of patients with cancer and curative substances, deserves particular consideration [15].

Therefore, giving a brief but complete illustration of these considerations is the purpose of this review.

According to data from seven high-income countries [16], patients with cancer have a higher probability of survival today than in the past thanks to new treatments and to 'patient-centered medicine'. Patients with cancer often have clinical characteristics that make their treatment complex. For example, they often have co-morbidities, requiring the use of non-cancer medicines or supplements, and they may be very young or very old, requiring special care. These factors can negatively influence the safety profile of a cancer drug. The complexity of treating cancer is further increased by the recent availability of targeted drugs and immunotherapies. These treatments have profoundly improved the outcomes of patients with cancer, but many years after their marketing authorization are required for their safety profile to be completely defined. The complexity of oncology makes the recognition of ADRs, and their distinction from other non-drug-related conditions, difficult.

Cancer therapy is evolving, on one hand, toward extreme personalization, and on the other, toward ever greater complexity. Oncologists, when prescribing cancer medicines, must take into consideration that a tumor's molecular heterogeneity (i.e. different parts of the same tumor having different genetic changes) can affect its response to treatment. Therefore, cancer therapy today often involves a combination of standard chemotherapy, radiotherapy and targeted therapy with biologic agents (including biosimilars), endocrine agents and growth factors.

In the initial period of a drug's marketing, most of the safety information contained in the medication package inserts derives from clinical trials that investigated safety and efficacy in controlled settings. These trials test drugs on relatively small samples of highly selected patients (i.e. fulfilling restrictive inclusion criteria) and monitor the safety and outcomes for relatively short periods of time [17]. Therefore, the safety information from clinical trials may not accurately reflect the safety profile a drug will have in clinical practice. Furthermore, in oncology, the desire to provide patients with the most recently approved treatments clashes with the need

to comprehensively collect safety data on these treatments. Thus, some cancer medicines are used clinically without a clearly defined risk-benefit ratio and with an unknown risk of AEs in the general population [18].

Although overall survival remains the gold standard for drug approval, the option of expedited programs, such as accelerated approval, may be considered if it is like to be significant for other intermediate – but essential- clinical endpoints, such as progression-free survival, reduction in tumor size or improvement in cancer-related symptoms [19]. In this regard, it is crucial to note that accelerated approvals raise numerous doubts and problems, as they are mainly based on the reduction of tumor size, on the objective response and mitigation of disease burden. These outcomes do not necessarily constitute significant clinical results (it may not imply benefits on overall survival). Due to the limitations of this strategy, accelerated approval is conditional and requires post-approval studies confirming that significant clinical benefits outweigh the risks [20].

However, the safety or toxicity risks deriving by an expedited approval program are not the only reason for caution.

Real-world observations can help to understand better which type of subjects will benefit most from a new drug, thus extending the results to the general population.

A representative example is the story of gefitinib and erlotinib, originally approved with accelerated programs for patients with NSLC (non-small cell lung cancer) not selected for EGFR target mutations; after new study data and even a prudential withdrawal, erlotinib and gefitinib had a definitive approval, respectively in 2013 and 2015, for patients whose NSCLC tumors harbor EGFR replacement mutations [21,22].

Another positive example of accelerated approval was the extension of the use of ibrutinib in chronic lymphocytic leukemia (CLL) in second line treatment, based on a phase 1b-2 study that evaluated safety and efficacy of ibrutinib regimens [23]. Other clinical trials that examined progression-free survival and overall survival have confirmed Ibrutinib's results [24,25].

So, after market authorization of a new drug, safety monitoring is required to understand its long-term safety. Post-authorization studies should be done in larger, more heterogeneous groups of patients, including patients with comorbidities, as they may respond differently and may have different ADRs than the patients who were enrolled in pre-authorization clinical trials [26].

2.1. ADRs from cancer therapy

Adverse effects of cancer therapies are concerning. They may require a change in drug dosage or drug withdrawal, compromising the effectiveness of the treatment [27]. More important, they are detrimental to the health of patients. According to one recent European study, an ADR caused or contributed to the need for hospitalization in 21.5% of cancer patients and, of these, 53.3% were caused by a systematic cancer therapy and 45.4% by non-tumor medications [14]. This study also found that in 89.3% of hospitalization cases, the ADRs were predictable and only 37.4% were unavoidable (using Hallas Criteria). The 21.5% rate of ADR-related hospitalization in cancer patients is much higher than the 6.5% reported for all ADR-caused hospital admissions [28].

Targeted therapies, which interfere with specific molecules involved in tumor progression, growth and spread, cause less specific ADRs than chemotherapy does [29]. These less specific ADRs include skin toxicity, altered blood counts, neurologic symptoms and mucositis, which have a more rapid onset than those caused by chemotherapy because they are triggered by autoimmune reactions or hypersensitive responses [30,31].

To assess the incidence of ADRs in clinical practice, our hospital (Centro di Riferimento Oncologico di Aviano – IRCCS) conducted a prospective observational study of more than 150 cancer patients undergoing targeted therapies (in monotherapy) [32]. The study compared observed ADRs, defined according to MedDRA, to those reported in the medications package inserts, and found notable differences. For example, among patients taking sorafenib, neuropathy was experienced by 40% (95% CI, 18.5%-61.5%) and skin desquamation by 35% (95% CI, 14.1%-55.9%), while the reported incidence for these ADRs is 1%-10%. Among patients taking sunitinib, hypothyroidism was experienced by 96.3% (95% CI, 89.2%-100%) and musculoskeletal pain by 55.6% (95% CI, 36.8%-74.3%), while the reported incidence for these ADRs is 1%-10%. This study also revealed new ADRs not reported in the medications package inserts (Table 1). These included hyperglycemia and hypercholesterolemia in patients treated with lenalidomide or sorafenib, hypomagnesemia in patients who took bevacizumab, and neutropenia in patients on cetuximab.

In addition to assessing the safety profile of these targeted therapies, the study [32] highlighted the importance of educating medical professionals and patients about pharmacovigilance in order to reduce the detrimental phenomenon of underreporting. Patients enrolled in the study, who were contacted once a month, were more involved and more open to communicating any ADRs. Therefore, the number of spontaneous reports increased by up to 124% compared to those collected at the hospital prior to the study.

2.2. Underreporting of ADRs

Spontaneous reporting by the public or health professionals is the most used and effective method for collecting drug safety data [3]. Bennet et al. [33] found that doctors were motivated to report AEs for five main reasons: public health, scientific curiosity, desire to disseminate important information, ethics, and a relative involved.

Table 1. ADRs of cancer therapy observed in clinical practice but not listed on medication package inserts, modified from [32].

Drug	Patients treated, n	ADR	Cases, n (%)	95% CI
Lenalidomide	14	Hypercholesterolemia	4 (28.6)	4.9–52.2
		Hyperglycemia	7 (50.0)	23.8–76.2
Sorafenib	20	Hypercholesterolemia	3 (15.0)	0.0–30.6
		Hyperglycemia	5 (25.0)	6.0–44.0
Bevacizumab	54	Hypomagnesemia	6 (12.2)	3.1–21.4
Cetuximab	12	Neutropenia	3 (25.0)	0.5–49.5

Underreporting of ADRs by doctors is, according to Inman [34], due to several factors, such as fear of making mistakes, lack of time, fear of legal action, preference to publish case reports of ADRs than to follow pharmacovigilance reporting procedures, ignorance of reporting procedures, and belief that drugs on the market are completely safe. Although ADRs reported in cases reports are ultimately detectable by the pharmacovigilance system, a more complex detection procedure is needed than that for spontaneous reporting. Furthermore, clinicians may consider a drug's toxicity to be 'normal' and inevitable [35]. The clinical severity and prognosis of a tumor affect their perception of the risk/benefit ratio of a treatment, so oncologists may consider ADRs of secondary importance to the disease [7]. They may also confuse an ADR with a disease manifestation, such as fatigue, neutropenia, vomiting, mucositis, stomatitis, and hair loss [36]. Finally, they may also not report an ADR to hide their feelings of guilt for having caused a patient toxicity by prescribing a cancer medicine with a narrow benefit-risk ratio [34].

Cancer patients may also have difficulty identifying the AA that need to be reported. If uneducated, they may attribute their symptoms to their comorbidities or confuse them with the 'normal' effects of treatment [36].

Overall, underreporting leads to the underestimation of the frequency of ADRs. The effect is a discrepancy between the known, published safety profile and the actual one, and this difference impacts on public health.

2.3. Polypharmacy and ADRs in oncology

Chemotherapy regimens often involve several different classes of drugs. Cancer patients, in addition to their cancer therapy, also often receive palliative and analgesic therapies, antiemetics, and complementary and alternative medicines to help manage ADRs. The assumption of complex combinations of medicines, involving multiple drugs, is called 'polypharmacy' [37]. Polypharmacy increase the risk of interactions among drugs or between drugs and other products, including natural ones. A recent retrospective observational study [38] found that one in four patients treated with parenteral antineoplastic drugs had at least one clinically relevant, potential drug-drug interaction; often the drug combinations were already known to be contraindicated. Furthermore, patients often consider natural products and food supplements (CAM – complementary and alternative products) as completely safe, without understanding that those molecules can interact with chemotherapy, increasing the risks originating from polypharmacy [39].

In oncology, the problem is even more relevant, since only in very few cases will cancer patients be treated with a single medication. All cancer patients have treatment programs that include a large number of medications which exceeds five units (chemotherapy or targeted therapies, accessories and palliative drugs), thus falling entirely within the definition of 'polypharmacy' [40].

Current knowledge and international pharmacovigilance systems provide all the tools and algorithms necessary to perform a causality assessment and detect new potential toxicity signals. However, in oncology, this step is for the most part still immature, due to the very high level of underreporting of individual adverse events. Once we can overcome, this phenomenon, it will be possible to use all technological and statistical tools fully.

The recordsets of adverse events in function of new signal detection are analyzed by observing the profile of the clinical and pharmacological aspects described in the literature (signal validation), the plausible temporal relationship with the intake of drugs and other criteria such as rechallenge or the possibility of attributing the adverse event to other diseases or drugs (signal evaluation) [41].

In polypharmacy, pharmacodynamic and pharmacokinetic interactions can be dangerous to patients and may reduce the effectiveness of therapy. One drug (or natural product) can influence the metabolism of other compounds, by activating or inhibiting an enzyme, or modify the absorption of other drugs [42]. Molecularly targeted therapies induce a variety of individual pharmacogenetic responses, which may exacerbate drug-drug interactions. For example, the cellular uptake or metabolism of a drug may be affected by polymorphisms in the genes encoding transporters or metabolic enzymes, leading to differences in efficacy and toxicity in different patients [43]. Knowledge about the frequency of alleles for these polymorphisms in particular ethnic groups can be used by local health authorities to estimate the risk of ADRs and to take action to prevent them. For example, in Singapore, the frequency of polymorphisms inhibiting irinotecan metabolism, leading to neutropenia, was higher in persons of Indian descent than in other ethnic groups, leading health authorities to recommend that Indian patients receive lower doses of the drug [44].

2.4. ADRs in elderly cancer patients

The increase in life expectancy in the past century has led to an increase in elderly patients with multiple comorbidities, including cancer. As life is prolonged, physiological changes occur (e.g. cardiovascular insufficiency, metabolic problems and kidney failure) that affect the efficacy and toxicity of drugs, requiring adaptations of therapeutic regimens and drug dosages.

Elderly cancer patients are often in polypharmacy. According to a population-based study from Scotland, 24.0% of patients aged ≥80 years took ≥10 drugs concomitantly, compared to 0.3% of patients 20–29 years of age [45]. Thus, elderly cancer patients are at greater risk of drug-drug interactions (or drug-natural product interactions). Alkan et al. estimated that nearly one third of the elderly cancer patients are exposed to the risk of severe drug interactions and potentially inappropriate medications (PIMs) [46].

Moreover, elderly cancer patients often have problems with compliance, especially of drug therapy that is usually taken orally in the home setting [47]. It is therefore more difficult to distinguish ADRs in elderly cancer patients from symptoms of existing conditions, complicating treatment decision making. This situation is not helped by the fact that, by design, most clinical trials exclude older adults and people with comorbidities [48].

3. Drugs for pediatric cancer: legislation and challenges in drug development and post-marketing pharmacovigilance

Today, 80% of all childhood cancers are curable in western countries [49], but 20% of children still die from some cancers with very poor outcomes that are difficult to treat with conventional chemotherapy [50]. Unfortunately, many pediatric cancers do not benefit from advances in targeted therapies, as many adult cancers did. For this very reason, the main challenge in pediatric oncology is to design successful strategies that may increase the development of innovative drugs for specific pediatric malignancies, based on mechanism of action, to improve survival rates in cancers with poor prognosis. Furthermore, including pediatric patients in clinical trials raises ethical and statistical problems. There is widespread use of off-label uses and, in general, the prescribers are not motivated to report ADRs to avoid implications or family complaints.

Lesson learned from the thalidomide disaster in the 1960 s compelled the pharmacovigilance system to provide greater attention to the health of children by collecting information on the use of drugs in this particular population. A review by Sachs et al. [51] highlighted that only 46% of medications package inserts have information on the pediatric use of the drug. This lead to a potentially high rate of off-label use of drugs in this population [52], for example when the SPCs lack description about licensed clinical indications for childhood and adolescents.

To support pharmaceutical companies in developing drugs for the pediatric population, both the US Food and Drug Administration (FDA) and EMA have implemented pertinent legislation to govern FDA and EMA actions, respectively. These include, in the United States, the 1997 FDA Administration Modernization Act, the 2002 Best Pharmaceuticals for Children Act, and the 2003 Pediatric Research Equity Act (PREA). The latter two legislative acts are complementary to each other and aim to increase the safety and efficacy of drugs, including oncological drugs, used in the pediatric population, in part by collecting information about the pediatric use of drugs. In the U.S.A., approval of drugs for pediatric use is responsibility of the FDA's Pediatric Review Committee [53]. The Pediatric Advisory Committee serves to encourage the reporting of ADRs in the pediatric population [54].

In Europe, the European Parliament established in 2006 the Pediatric Regulation, which came into force in 2007. This regulation requires pharmaceutical companies to provide a 'pediatric investigation plan' (PIP) at the end of adult pharmacokinetic trials [55]. The PIP reports the planned studies for evaluating the safety and efficacy of a drug in children. However, costs, recruitment difficulties, and ethical obstacles make it challenging to conduct pediatric clinical trials. Finally, EMA decides whether that drug can be approved for pediatric use. Furthermore, European Directive 2010/84/EU established measures to facilitate pharmacovigilance via Good Pharmacovigilance Practices. These guidelines include a chapter dedicated to the pediatric population [56].

This legislation from both the United States and European Union highlights the importance of reporting ADRs in children, to discover new ADRs or differences in the frequency in unwanted events between adults and children. Pharmaceutical care in pediatric patients is demanding because the majority of drugs have been essentially licensed for use in adults. Even if the FDA and EMA are developing strategies to improve the quality of trials, starting right from the initial phase 1 *targeted trials* [57], pediatricians have often no alternative but to prescribe drugs which are not officially licensed for pediatric use or to write *off-label* adult prescriptions, adjusting the dosage. Formulations suitable for use in children at the appropriate doses are lacking. Studies have shown that the off-label use of drugs in children is associated with a higher rate of ADRs than observed when the drugs are used according to official recommendations [58–60]. Additionally, while the use of approved drugs is monitored by a well-coded system of pharmacovigilance, the process of collecting information on ADRs related to the unauthorized use of drugs and extemporaneous preparations is not well defined. Safety monitoring was significantly improved by the current EU regulation [61] in pharmacovigilance that modified the definition of 'adverse reaction' to include off-label use. The design of clinical trials involving children, especially regarding rare diseases like childhood cancer, is complicated due to the small number of patients that can be enrolled and to the heterogeneity of this population which results from their changing physiological characteristics as they grow. These physiological changes are reflected in different pharmacokinetic, pharmacodynamic and pharmacogenetic patterns.

So, the current approach in pediatric oncology (and hematology-oncology) in European and other western countries is to build large international collaborative networks to promote pediatric oncological research for innovative therapies that are the key to fight pediatric cancer with poor diagnosis [62]. Such an approach leads to avoiding unnecessary movements and dispersion of resources, to find better treatments for the child, and at the same time, harness existing expertise and facilitates patient access to innovative therapies [63]. By organizing international clinical trials, global networks have made considerable progress in cure-rates. For example, innovative target therapies, such as blinatumomab or bortezomib in pediatric cancer, have been introduced only recently for the earlier treatment regimens of acute lymphoblastic leukemia (ALL). Additionally, it is fundamental to foster research trials with the best efficacy and safety profile oncology drugs.

Anticancer drugs initially developed for administration in adults, are often adapted for pediatric cancer when the disease occurs in both. Until now, the European Pediatric Regulation and the PREA did not require the development of pediatric investigation based on the potential relevance of the mechanism of action of the drug onto pediatric malignancies. In the US, from August 2020 with Race for children act, FDA will require pediatric studies for adult cancer drugs whenever they match with the biology of pediatric malignancies.

Many pediatric cancers have a different biological mechanism than adult cancers, so it is necessary to invest in network researches to find target drugs against specific molecular biomarkers for pediatric cancer, designing particular pre-clinical and clinical studies [64,65]. Pre-clinical studies should evaluate the potential toxicity on the organs in children. Since PIP is applied to assess drugs already approved in adults, and therefore it is based on adult molecular targets, it is advisable first to perform PD/PK modeling assessments to predict the

appropriate pediatric doses. Generally, the administration of innovative therapies involves pediatric patients whose cancer have relapsed or who are refractory to conventional chemotherapy.

The current curative chemotherapy treatments for childhood cancer often results in long-term side effects in survivors and reduced their quality of life. Therefore, long-term follow-up is of great importance. Importantly, while standardized surveillance guidelines for late side effects of childhood cancers were mostly missing until 2015 [66], the *PanCareSurFup Working Group* approved recommendations for appropriate long-term follow-up of childhood and adolescent survivors [49,66].

In the complex scenario in pediatric cancer treatment, oncology pharmacists are increasingly recognized for their role in ensuring that therapies are safe, effective and cost-effective [67].

The presence of the clinical pharmacist in pediatric oncology is significant, more than in other fields, because of the risk of drug toxicity and the extensive use of off-label prescriptions. Oncological drugs have a narrow therapeutic window, and a small change in the dosage can cause a significant variability in their toxicity. In pediatric oncology, the drug dose is proportionally higher than that for adults, and treatment regimens include many anticancer drugs. Therefore, therapy monitoring by the clinical pharmacist is fundamental to decrease ADRs.

Active pharmacovigilance by the pharmacist consists mainly of medication review, evaluation of the appropriateness of prescriptions for individual patients, and initiatives undertaken to empower caregiver awareness about drug safety in children. Oncology pharmacists should promptly assess reported side effects, and monitor patients for the assumption of other drugs, foods or complementary medications that could interact with a cancer medicine. Furthermore, active pharmacovigilance is crucial to ensure medication safety and to decrease the phenomenon of under-reporting.

The problem of compliance with oral oncological treatment is relevant in pediatric oncology because the administration of oral therapies, as maintenance therapy, lasts for a prolonged time. For this reason, patients, in particular adolescents, have often the perception of being healthy and forget to take the treatment, causing a reduced efficacy and an increased risk of relapse [68].

Pharmacist's intervention can facilitate patients' compliance and their treatment plans, by instructing on how to take the drugs, how to prevent interactions with other therapies and foods, how to recognize the onset of ADRs, how to report them to their physicians or pharmacists, and how to manage them. Indeed, the clinical pharmacist can monitor the pills taken by the patient before dispensing another drug pack.

The clinical pharmacist may perform individualized dosing and therapeutic drug monitoring, optimizing a patient's drug administration. The designated clinical pharmacist should participate in ward rounds and meetings to maximize the pharmacovigilance service [69].

In conclusion, the main challenge of modern pharmacovigilance in pediatric oncology is to find the best balance between the need for childcare, the awareness of drug toxicity and the awareness of the doctor who needs to know that he often uses registered drugs for adults and not for children and adolescents.

4. Digital tools and statistical models for pharmacovigilance. What innovations could we expect for oncology?

Information technology has significantly improved the efficiency and effectiveness of all aspects of pharmacovigilance. In general, ADR signaling methods, causality assessment and signal detection applied for pharmacovigilance in general clinical practice are the same also for oncology. The relevant problem for oncology is that the underreporting phenomenon is much more amplified, since chemotherapy-related toxicity is relevant, and therefore it is considered almost 'a price to pay'.

4.1. AE reporting

AE reports are fundamental sources of safety data for pharmacovigilance. It is worth mentioning briefly some innovative methods of synthesis and analysis in pharmacovigilance, giving some specific examples for oncology:

- **Cognitive computing**, also called machine learning, is 'a field of study that gives computers the ability to learn without being explicitly programmed' [70]. Cognitive computing algorithms can automate several activities in pharmacovigilance, especially the routine tasks of case management, and therefore may reduce the overall costs and time of coding and labeling AE reports.
- **Natural language processing (NLP)** is a part of cognitive computing in which computers automatically understand, interpret, and manipulate human language (such as speech and narrative text) for the extraction and structuring of data. NLP has recently been implemented in the WEB-RADR (Recognizing Adverse Drug Reactions) project, whose aim is to develop a process for AE recognition in social media [71]. NLP may improve the identification and readability of AE reports from unstructured sources. However, the WEB-RADR consortium recommends that social media not be used as a primary source of AE reports due to the poor quality of the data [72].
- **Robotic process automation** is the automation of manual repetitive steps that do not require human intervention (e.g. decision making). This technology reduces the time for transcription and reconciliation of data.
- **Cloud infrastructure**. Most marketing authorization holders have begun to place their applications and data on internet-based computing infrastructures called 'clouds'. Cloud computing allows multiple users in different locations to access and use shared data. The benefits of cloud infrastructures are cost efficiency, process standardization, information security, and resilience.

4.2. AE report surveillance

AE report surveillance depends on data both in the clinical safety databases of pharmaceutical companies and from spontaneous post-marketing AE reporting. Signal detection and validation are so important that EMA has established continuous monitoring (in EudraVigilance) as a legal requirement

[73]. Other data come from the FDA's Adverse Event Reporting System (AERS), WHO's VigiBase, and other sources (e.g. government registries, scientific publications, conference abstracts, poster presentations, electronic health records, social media). Large databases of adverse drug reactions serve as valuable data sources for pharmacovigilance activities, and in particular for the detection of new safety signals. However, databases are often insufficiently structured and can be very different from each other; furthermore, they may differ in the syntax and meaning of specific terms. This makes univocal evaluation of the correlations between use of a drug and the onset of an adverse reaction very complex. To overcome this problem, new pharmacovigilance tools are developed based on the following digital technologies:

- **Data mining** is the computerized analysis of information extracted from large data sets. The FDA has demonstrated that data mining is useful in drug safety signal detection [74]. In oncology, data mining contributed in favoring detection of many important signals, including the association between atypical antipsychotics and pituitary tumors [75].

- **Advanced predictive statistics**. Quantitative analysis of AE reports is routinely done in pharmacovigilance through the use of several disproportionality methods to identify statistical associations between products and events, leading to the calculation of proportional reporting ratios, reporting odds ratios, information components or empirical Bayes geometric means [76]. For instance, Perino and colleagues performed a disproportionality analysis in Vigibase to assess the strength of association between cardiac failure and azacytidine [77]. Another recent application of disproportionality analysis allowed to identify strong signals of ototoxicity involving the most recent oncologic therapies (such as monoclonal antibodies and tyrosine kinase inhibitors) [78].

Disproportionality analysis represents a valuable tool to identify drug safety signals, but has several limitations, since it is usually based on cumulative data and therefore does not provide direct insight into temporal changes in the frequency of AE reports. To overcome this limitation, advanced statistical methods have been developed to monitor frequency changes over time, for example in the case of small recordsets of individual cases, or when drugs have already a well-defined toxicity profile, or finally, in presence of other elements of concern [79]. In addition, emerging research investigates new statistical methods that aim to reduce confounding factors such as concomitant drugs and/or comorbidities. Interestingly, an innovative approach combines the analysis of disproportionality with features such as the number of structured and well documented ADRs reports, the number of recent reports and the geographical spread of cases [80]. As knowledge increases regarding biological pathways and molecular targets that are involved in the onset of ADRs [81], it should become possible to refine the prediction of ADRs. For example, Patras de Campaigno and colleagues [82] determined the potential risk of cardiac failure for 15 anticancer protein kinase inhibitors combining disproportionality analysis with pharmacodynamics data. In another study, Low et al. implemented a quantitative structure-activity relationship model to predict the drugs associated with Stevens-Johnson syndrome [83]. Even if more work is needed to test the applicability of advanced predictive statistics in a real-world setting, these approaches may give rise to new hypotheses, allowing to further refine the identification of cellular targets involved in ADR caused by anticancer drugs, as well as from other cellular targets involved in ADRs.

4.3. Causality and risk assessment

This step determines whether there is an ADR and what is the risk to public health. Digital tools supporting causality and risk assessment include:

- **Safety assessment software and platforms**. Today, many commercial software platforms exist for managing data captured from AE reports to use in benefit-risk assessment.
- **Real-world safety data analytics**. Researchers have been exploring the use of real-world safety data analytics to accelerate pharmacovigilance data flow and big data collection (e.g., data from social media, electronic health records, insurance claims) [84]. One example is Hadoop, an open-source framework that enables data analysts to store massive quantities of data in an organized and easier manner for processing and analyzing multiple data sets [85].

4.4. Risk minimization and patient involvement programs

This step consists of communicating, preventing and managing a specific safety risk to patients, health professionals, and other stakeholders. A new frontier of research is to exploit artificial intelligence (AI) to identify drug-related risks and to communicate them more readily to patients, healthcare practitioners, and other stakeholders. The risks might be communicated through mobile apps, wearable devices or clinical decision support systems. Thus, healthcare practitioners can take these risks into account while devising treatment strategies and prescription options [86].

Mobile applications and wearable devices are examples of a relatively new technology that is evolving rapidly and may provide vast opportunities for drug safety information for pharmacovigilance. The rise of innovative health care data sources such as wearable devices and mobile health (mHealth) applications has posed some challenges in terms of characterizing heterogeneous AE data that could be structured or unstructured. The power of data from wearable and mHealth apps depends on the degree to which these technologies successfully manage the raw data, extract valuable information, transform that information into knowledge, and

enable clinical decision making and risk minimization strategies [87,88].

Although numerous challenges remain, the promise and opportunity for advanced technologies to make further contributions to pharmacovigilance efforts are evident. Improved analytical methods, tools, and data sources used in pharmacovigilance are still in the early stages of development and are likely to further advance the use of a large volume of data (big data) for pharmacovigilance in the future. The strategic use of big data represents a new frontier of research for pharmacovigilance and is of paramount importance especially for the safety of cancer drugs, a category of drugs with high complexity.

5. Conclusions

Pharmacovigilance saves lives, but it has costs for public institutions and companies. Patient reporting of ADRs adds new information from new perspectives. This review identified gaps in knowledge that should be addressed to improve our understanding of the full potential and drawbacks of patient reporting. Other factors such as providing general education on pharmacovigilance are seen as effective measures. Pharmacovigilance must demonstrate the ability to understand technological and scientific-clinical progress to show that it is in step with the times. On the other hand, public institutions and hospitals should invest in the training of specialized pharmacovigilance personnel and should provide adequate working time for the implementation of such applications.

6. Expert opinion

6.1. Challenges of modern pharmacovigilance

6.1.1. Heterogeneity

The international system which manages pharmacovigilance has made tremendous progress over the past 50 years. However, some challenges remain unresolved. The first challenge is to reduce the heterogeneity of AE reporting systems among countries. Furthermore, the definition of ADRs, according to WHO, has not changed over time, but monitoring and reporting ADRs in the various health and political-social realities have changed thanks to increased health professionals and patients' awareness. Heterogeneity complicates communication and the interpretation of data [89]. This 'noise' can create bias in the early detection of serious ADRs and consequently, in unclear generation of signals which lead to actions promoted by regulatory authorities.

6.1.2. Underreporting

Another challenge is understanding and finding methods to overcome the phenomenon of underreporting. This phenomenon is common in both hospital and community settings [90]. As already described above, the fundamental causes of underreporting are essentially two: a general reliance by health professionals to be involved in recording individual clinical cases which may have legal implications; a still poor cultural sensitivity in recognizing the powerful, intrinsic potential harm related to the use of drugs, especially in intensive hospital use. And we can't avoid citing the lack of health professionals' confidence in believing that there could be a benefit for the patient by using *appropriate management of specific ADRs*.

6.1.3. Costs

The costs of managing AEs can be significant, and thus treatments with less probability of causing severe ADRs are valuable. They are originated not only by management of adverse events (direct costs), but also to indirect consequences, for example re-admission to hospital or secondary co-morbidities (intolerance, allergies to cite the simpler examples). If the clinical Institutions included an assessment of the costs caused by the management of the ADRs as a specific item within the global hospital economic management, this could increase the awareness of the staff, thus simultaneously favoring at the same time more objectives: quality of care as more attention is given to the appropriate management of ADRs without resources waste, decrease in underreporting phenomenon and cost control.

Furthermore, while the costs for the management of negative clinical outcomes are preventable in most clinical contexts, in oncology the potential toxicities (and costs) are not the main reason for choosing among the alternatives [91].

For this reason, the actions promoted by clinical oncology pharmacist must go in the direction of improving knowledge about *specific management* of all the different ADRs detected following cancer drug administration. Too often an adverse event in oncology is detected and recorded, but not always health professionals are able to give promptly a therapeutic response for the care of the single patient.

6.2. Opportunities for modern pharmacovigilance

6.2.1. Patient participation

Having patient information automatically populated from the dispensing clinical prescription software into an ADR data field or report, associated with reminder questions, is an efficient way to report ADRs [92]. Patient participation and awareness of the whole care program are increasing. Patients' spontaneous reporting of ADRs are not expected to replace the individual case reports (ICRs) recorded by health professionals in the official regulatory platforms (e.g. AERS, EudraVigilance), but are an additional source of information about a patient's symptoms [93]. ADRs reported by patients describe a personally experienced event and add information that otherwise would not be reported [94,95]. They provide a detailed description of ADRs when compared with health professionals' reporting. In addition, patients describe the severity and also subjective impact of ADRs on their daily life, complementing information derived from professionals. However, there are limitations due to patients' inaccurate use of terminology, especially when there is an exaggerated use of the internet 'social' platforms. making records potentially very confounding in the generation and analysis of pharmacovigilance signals.

6.2.2. Personalization

The identification of molecular targets favored both the personalization of most of the therapies, and the overcoming of the classic chemotherapy strategy. Markers can be genomic, which are involved into pharmacodynamic or pharmacokinetic mechanisms; immunogenetic, involved in immune system and immunity-related or auto-immunity reactions, or due to rare individual variants.

6.2.3. Use of predictive models to study pathway-ADR correlations

If the newly discovered markers are used in clinical practice, we will move from 'observational and descriptive' pharmacovigilance to 'predictive' pharmacovigilance, which is the true meaning of this discipline.

The prediction of drug-related AEs may be improved by the use of artificial intelligence and data mining. Several tools can be helpful, for example, in building prediction models for drug-drug interactions [96,97]. The resulting warnings can be included in drug data sheets to facilitate the safe and optimal use of these drugs and be used to predict side effects during drug design [94]. The possibility of early detection of the risk factors, involves the double advantage of preventing AEs and avoiding the consequential costs for their treatment.

Acknowledgements

The authors thank Valerie Matarese, PhD, of UpTo infotechnologies for providing medical writing support.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Diana Crestan http://orcid.org/0000-0003-0809-6601
Sara Francescon http://orcid.org/0000-0001-8042-7773
Giulia Fornasier http://orcid.org/0000-0003-3055-7080
Paolo Baldo http://orcid.org/0000-0002-5106-7120

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. WHO. Pharmacovigilance [Internet]. WHO; [cited 2020 Jan 20]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
2. Safety of Medicines. A guide to detecting and reporting adverse drug reactions - why health professionals need to take action: glossary [Internet]. [cited 2020 Mar 2]. Available from: https://apps.who.int/medicinedocs/en/d/Jh2992e/2.html
3. Patrignani A, Palmieri G, Ciampani N, et al. Mancata segnalazione di reazioni avverse ai farmaci: un problema che riguarda anche farmaci sottoposti a monitoraggio addizionale. Dati preliminari di un singolo centro sui nuovi anticoagulanti orali. G. Ital. Cardiology. 2018;19:54–61.
4. Common Terminology Criteria for Adverse Events (CTCAE). Protocol development | CTEP [Internet]. [cited 2020 Jan 20]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
5. MedDRA. [Internet]. [cited 2020 Jan 20]. Available from: https://www.meddra.org/
6. Kluetz PG, Chingos DT, Basch EM, et al. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Annu Meet. 2016;35:67–73.
7. Tuccori M, Montagnani S, Capogrosso-Sansone A, et al. Adverse reactions to oncologic drugs: spontaneous reporting and signal detection. Expert Rev Clin Pharmacol. 2015;8:61–75.
   • **It provides an overview of the management of spontaneous reports and criticality of under-reporting in oncology, providing the main reasons why oncologists do not report.**
8. ISOP. International society of pharmacovigilance [Internet]. [cited 2020 Jan 20]. Available from: https://isoponline.org/
9. Anonymous. EudraVigilance [Internet]. Eur Med Agency. 2018 cited 2020 Jan 20. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance
10. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human useText with EEA relevance.:26.
11. Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med. 2016;16:481–485.
12. Potts J, Genov G, Segec A, et al. Improving the safety of medicines in the European Union: from signals to action. Clin Pharmacol Ther. 2020;107:521–529.
13. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27:2758–2765.
14. Lavan AH, O'Mahony D, Buckley M, et al. Adverse drug reactions in an oncological population: prevalence, predictability, and preventability. Oncologist. 2019;24:e968–e977.
   • **Lavan et al report the implications of a cancer diagnosis in subjects presenting comorbidities and therefore undergoing polypharmacy, stressing the risk of drug-drug interactions and preventable ADRs that may lead to a hypothetical unnecessary hospitalization of the patient.**
15. Young JS, Simmons JW. Chemotherapeutic medications and their emergent complications. Hematol Oncol Clin North Am. 2017;31:995–1010.
16. Arnold M. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol [Internet]. 2020 Jan 29. Available from: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30456-5/fulltext
17. Seruga B, Sterling L, Wang L, et al. Reporting of serious adverse drug reactions of targeted anticancer agents in pivotal phase III clinical trials. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29:174–185.
18. Johnson JR, Ning Y-M, Farrell A, et al. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst. 2011;103:636–644.
19. Blumenthal GM, Kluetz PG, Schneider J, et al. Oncology Drug approvals: evaluating endpoints and evidence in an era of breakthrough therapies. Oncologist. 2017;22:762–767.
20. DiMagno SSP, Glickman A, Emanuel EJ. Accelerated approval of cancer drugs-righting the ship of the US Food and Drug Administration. JAMA Intern Med. 2019;179:922–923.
21. Kazandjian D, Blumenthal GM, Yuan W, et al. FDA approval of gefitinib for the treatment of patients with metastatic EGFR

mutation-positive non-small cell lung cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2016;22:1307–1312.
22. Modified indication for erlotinib in advanced non–small cell lung cancer - the ASCO Post [Internet]. [cited 2020 May 5]. Available from: https://www.ascopost.com/issues/november-10-2016/modified-indication-for-erlotinib-in-advanced-non-small-cell-lung-cancer/
23. Ahn IE, Farooqui MZH, Tian X, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018;131:2357–2366.
24. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018;379:2517–2528.
25. Tran PN, O'Brien S. The safety of Bruton's tyrosine kinase inhibitors for the treatment of chronic lymphocytic leukemia. Expert Opin Drug Saf. 2017;16:1079–1088.
26. Ioannidis JPA. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med. 2009;169:1737–1739.
27. Barthélémy P, Asmane-de la Porte I, Meyer N, et al. Adherence and patients' attitudes to oral anticancer drugs: a prospective series of 201 patients focusing on targeted therapies. Oncology. 2015;88:1–8.
28. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329:15–19.
29. Baldo P, De Paoli P. Pharmacovigilance in oncology: evaluation of current practice and future perspectives. J Eval Clin Pract. 2014;20:559–569.
30. Baldo P, Fornasier G, Francescon S, et al. Toxicities and adverse drug reactions experienced during anticancer treatment: it is desirable to consider the problem within the international system of pharmacovigilance. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33:2824–2825.
31. Kroschinsky F, Stölzel F, von Bonin S, et al. New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. Crit Care Lond Engl. 2017;21:89.
32. Fornasier G, Taborelli M, Francescon S, et al. Targeted therapies and adverse drug reactions in oncology: the role of clinical pharmacist in pharmacovigilance. Int J Clin Pharm. 2018;40:795–802.
•• **This prospective observational pilot study underlines the importance of having active pharmacovigilance programmes in order to identify the real incidence of ADRs and the possible presence of new ADRs not reported in SmPC**
33. Bennett CL, Schooley B, Taylor MA, et al. Caveat medicus: clinician experiences in publishing reports of serious oncology-associated adverse drug reactions. PloS One. 2019;14:e0219521.
34. Inman WH. Attitudes to adverse drug reaction reporting. Br J Clin Pharmacol. 1996;41:434–435.
35. Pitts PJ, Louet HL, Moride Y, et al. 21st century pharmacovigilance: efforts, roles, and responsibilities. Lancet Oncol. 2016;17:e486–e492.
36. Baldo P, Fornasier G, Ciolfi L, et al. Pharmacovigilance in oncology. Int J Clin Pharm. 2018;40:832–841.
37. Onder G, Marengoni A. Polypharmacy. JAMA. 2017;318:1728.
38. Castro-Manzanares M, Do Pazo-Oubiña F, Rodríguez-Rincón RM. Prevalence of potential drug-drug interactions in outpatients on treatment with parenteral antineoplastic drugs. Int J Clin Pharm. 2019;41:1429–1433.
39. Clairet A-L, Boiteux-Jurain M, Curtit E, et al. Interaction between phytotherapy and oral anticancer agents: prospective study and literature review. Med Oncol. 2019;36:45.
40. Park H-Y, Ryu H-N, Shim MK, et al. Prescribed drugs and polypharmacy in healthcare service users in South Korea: an analysis based on National Health Insurance Claims data. Int J Clin Pharmacol Ther. 2016;54:369–377.
41. UMC. Uppsala Monitoring Centre [Internet]. [cited 2020 Apr 29]. Available from: https://www.who-umc.org/
42. Akbulut M, Urun Y. Onco-cardiology: drug-drug interactions of antineoplastic and cardiovascular drugs. Crit Rev Oncol Hematol. 2020;145:102822.
43. Bertholee D, Maring JG, van Kuilenburg AB. Genotypes affecting the pharmacokinetics of anticancer drugs. Clin Pharmacoki-net. 2017;56(4):317–337.
44. Sung C, Lee PL, Tan LL, et al. Pharmacogenetic risk for adverse reactions to irinotecan in the major ethnic populations of Singapore: regulatory evaluation by the health sciences authority. Drug Saf. 2011;34:1167–1175.
45. Guthrie B, Makubate B, Hernandez-Santiago V, et al. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med. 2015;13:74.
46. Alkan A, Yaşar A, Karcı E, et al. Severe drug interactions and potentially inappropriate medication usage in elderly cancer patients. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2017;25:229–236.
47. Krikorian S, Pories S, Tataronis G, et al. Adherence to oral chemotherapy: challenges and opportunities. J Oncol Pharm Pract [Internet]. 2018 [cited 2020 Feb 28]. Available from: https://journals.sagepub.com/doi/10.1177/1078155218800384
48. Van Spall HGC, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297:1233–1240.
49. Michel G, Mulder RL, van der Pal HJH, et al. Evidence-based recommendations for the organization of long-term follow-up care for childhood and adolescent cancer survivors: a report from the PanCareSurFup Guidelines Working Group. J Cancer Surviv Res Pract. 2019;13:759–772.
50. Aldape K, Brindle KM, Chesler L, et al. Challenges to curing primary brain tumours. Nat Rev Clin Oncol. 2019;16:509–520.
51. Sachs AN, Avant D, Lee CS, et al. Pediatric information in drug product labeling. JAMA. 2012;307:1914–1915.
52. Food and Drug Administration (FDA). Best pharmaceuticals for children actand pediatric research equity act. 2016. Available from: https://www.fda.gov/media/99184/download
53. Food and Drug Administration (FDA). [Internet]. Available from: https://www.accessdata.fda.gov/scripts/cderworld/index.cfm?action=newdrugs:main&unit=4&lesson=1&topic=8
54. Food and Drug Administration (FDA). [Internet]. 2019. Available from: https://www.fda.gov/files/advisory%20committees/published/lyrica-pediatric-postmarketing-pharmacovigilance-review.pdf
55. Anonymous. Paediatric investigation plans [Internet]. Eur Med Agency. 2018 [cited 2020 Jan 20]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans
56. Tomasi PA, Egger GF, Pallidis C, et al. Enabling development of paediatric medicines in Europe: 10 years of the EU paediatric regulation. Paediatr Drugs. 2017;19:505–513.
57. Cohen JW, Akshintala S, Kane E, et al. A SYSTEMATIC review of pediatric phase I Trials in oncology: toxicity and outcomes in the era of targeted therapies. Oncologist. 2020. DOI:10.1634/theoncologist.2019-0615.
58. Gore R, Chugh PK, Tripathi CD, et al. Pediatric off-label and unlicensed drug use and its implications. Curr Clin Pharmacol. 2017;12:18–25.
59. Yackey K, Stukus K, Cohen D, et al. Off-label medication prescribing patterns in pediatrics: an update. Hosp Pediatr. 2019;9:186–193.
60. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr. 2005;164:552–558.
61. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal productsText with EEA relevance.:16.
62. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5–a population-based study. Lancet Oncol. 2014;15:35–47.
63. Fiagop. Il Piano Strategico SIOPE [Internet]. [cited 2020 Apr 29]. Available from: http://www.fiagop.it/?p=303

64. Pearson ADJ, Pfister SM, Baruchel A, et al. From class waivers to precision medicine in paediatric oncology. Lancet Oncol. 2017;18:e394–e404.
65. Hansford JR. Personalised medicine in paediatric oncology: ethical practice outside the clinical trial framework? J Paediatr Child Health. 2019;55:10–12.
66. Hjorth L, Haupt R, Skinner R, et al. Survivorship after childhood cancer: panCare: a European Network to promote optimal long-term care. Eur J Cancer Oxf Engl. 1990;2015(51):1203–1211.
•• **Lack of therapeutic innovation is a principal reason of failure to improve the cure rates of some cancers and may cause adverse long-term side effects of treatment in survivors. Over two-thirds of childhood cancer survivors experience long-term health problems which may be severe and reduce heavily their quality of life. The PanCare Network was set up in Europe with the aim to reduce the frequency, severity and impact of ADRs of anticancer treatment for pediatric survivors and in order to improve the care and quality of life of patients.**
67. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA. 1999;282:267–270.
• **Due to the complex scenario in pediatric cancer treatment and its associate supportive care, the hematology-oncology clinical pharmacists' contribution to the safe, effective and cost-effective therapeutics, as a member of multidisciplinary team, is increasingly recognized. This article highlights that the presence of the pharmacist inside a multidisciplinary team for the treatment of cancer may reduce by 66% the preventivable ADRs, in particular those due to prescribing errors.**
68. Linder LA, Wu YP, Macpherson CF, et al. Oral medication adherence among adolescents and young adults with cancer before and following use of a smartphone-based medication reminder app. J Adolesc Young Adult Oncol. 2019;8:122–130.
69. Bauters T, Vinent-Genestar J, Delaney J, et al. Role of the clinical pharmacist in a paediatric haemato-oncology stem cell transplantation ward. Eur J Hosp Pharm. 2014;21:309–312.
70. Samuel AL. Some studies in machine learning using the game of checkers. IBM J Res Dev. 1959;3:210–229.
71. WEB-RADR [Internet]. WEB-RADR. [cited 2020 Jan 29]. Available from: https://web-radr.eu/
72. van Stekelenborg J, Ellenius J, Maskell S, et al. Recommendations for the use of social media in pharmacovigilance: lessons from IMI WEB-RADR. Drug Saf. 2019;42:1393–1407.
• **Detecting the ADRs sets up a big challenge for oncology. Under-reporting is an issue, with patients sometimes more prone to sharing their experience of an ADR via social media channels than consulting their physician. The IMI's WEB-RADR project has bringed together patients, health professionals, pharmaceutical industries, and health regulators to develop a mobile application which allows patients to directly report ADRs and to receive evidence-based information on their medication treatment. The project was also helpful to detect new safety signals, to improve drug safety monitoring, and to assess the utility of advanced information technologies for pharmacovigilance activities.**
73. Guideline on good pharmacovigilance practices (GVP). Module IX – signal management (Rev 1).:25.
74. Duggirala HJ, Tonning JM, Smith E, et al. Use of data mining at the Food and Drug Administration. J Am Med Inform Assoc JAMIA. 2016;23:428–434.
75. Szarfman A, Tonning JM, Levine JG, et al. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. Pharmacotherapy. 2006;26:748–758.
76. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18:427–436.
77. Perino J, Mottal N, Bohbot Y, et al. Cardiac failure in patients treated with azacitidine, a pyrimidine analogue: case reports and disproportionality analyses in Vigibase. Br J Clin Pharmacol. 2020;86:991–998.
78. Favrelière S, Delaunay P, Lebreton J-P, et al. Drug-induced hearing loss: a case/non-case study in the French pharmacovigilance database. Fundam Clin Pharmacol [Internet]. 2020 Apr 29. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/fcp.12533
79. Xiao C, Li Y, Baytas IM, et al. An MCEM framework for drug safety signal detection and combination from heterogeneous real world evidence. Sci Rep. 2018;8:1–10.
80. Caster O, Juhlin K, Watson S, et al. Improved statistical signal detection in pharmacovigilance by combining multiple strength-of-evidence aspects in vigiRank. Drug Saf. 2014;37:617–628.
81. Zheng H, Wang H, Xu H, et al. Linking biochemical pathways and networks to adverse drug reactions. IEEE Trans NanoBiosci. 2014;13:131–137.
82. Patras de Campaigno E, Bondon-Guitton E, Laurent G, et al. Identification of cellular targets involved in cardiac failure caused by PKI in oncology: an approach combining pharmacovigilance and pharmacodynamics. Br J Clin Pharmacol. 2017;83:1544–1555.
83. Low YS, Caster O, Bergvall T, et al. Cheminformatics-aided pharmacovigilance: application to Stevens-Johnson Syndrome. J Am Med Inform Assoc. 2016;23:968–978.
84. Khosla S, White R, Medina J, et al. Real world evidence (RWE) - a disruptive innovation or the quiet evolution of medical evidence generation? F1000Res. 2018;7:111.
85. Dong X, Bahroos N, Sadhu E, et al. Leverage hadoop framework for large scale clinical informatics applications. AMIA Jt Summits Transl Sci Proc AMIA Jt Summits Transl Sci. 2013;2013:53.
86. Artificial intelligence in pharmacy: are you ready? | Clinical Drug information [Internet]. [cited 2020 Jan 29]. Available from: https://www.wolterskluwercdi.com/blog/artificial-intelligence-pharmacy-are-you-ready/
87. Osborn J, Ajakaiye A, Cooksley T, et al. Do mHealth applications improve clinical outcomes of patients with cancer? A critical appraisal of the peer-reviewed literature. Support Care Cancer. 2020;28:1469–1479.
88. Group BMJP. Algorithm based smartphone apps to assess risk of skin cancer in adults: systematic review of diagnostic accuracy studies. BMJ [Internet]. 2020 [cited 2020 May 5];368. Available from: https://www.bmj.com/content/368/bmj.m645
89. Bailey C, Peddie D, Wickham ME, et al. Adverse drug event reporting systems: a systematic review. Br J Clin Pharmacol. 2016;82:17–29.
90. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;29:385–396.
91. Formica D, Sultana J, Cutroneo PM, et al. The economic burden of preventable adverse drug reactions: a systematic review of observational studies. Expert Opin Drug Saf. 2018;17:681–695.
92. Li R, Curtain C, Bereznicki L, et al. Community pharmacists' knowledge and perspectives of reporting adverse drug reactions in Australia: a cross-sectional survey. Int J Clin Pharm. 2018;40:878–889.
93. Inácio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. Br J Clin Pharmacol. 2017;83:227–246.
94. Rolfes L, van Hunsel F, Wilkes S, et al. Adverse drug reaction reports of patients and healthcare professionals-differences in reported information. Pharmacoepidemiol Drug Saf. 2015;24:152–158.
95. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in europe: a review of recent observational studies. Drug Saf. 2015;38:437–453.
96. Zheng Y, Peng H, Zhang X, et al. Predicting adverse drug reactions of combined medication from heterogeneous pharmacologic databases. BMC Bioinformatics. 2018;19:517.
97. Zheng Y, Peng H, Ghosh S, et al. Inverse similarity and reliable negative samples for drug side-effect prediction. BMC Bioinformatics. 2019;19:554.