Adverse reactions to oncologic drugs: spontaneous reporting and signal detection.

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Summary

Oncology is one of the medical areas with the most active research on new drugs. New pharmacological entities frequently enter in the clinical arena and therefore the safety profile of anticancer products deserve continuous monitoring. However, only very severe and unusual suspected adverse drug reactions (ADRs) are usually reported, since cancer patients ~~have~~ develop ADRs very frequently and some practical selectivity must be used. Notably, a recent study was able to identify 76 serious ADRs reported in updated drug labels of oncologic drugs, and 50% (n=38) were potentially fatal. Of these, 49% and 58%, respectively, were not described in initial drug labels. The aims of this review are to provide an overview about spontaneous reporting of ADRs of oncologic drugs and to discuss ~~show~~ the available methods to analyze the safety of anticancer drugs using databases of spontaneous ADRs reporting.

Keywords

Introduction

Spontaneous reporting of adverse drug reactions (ADRs) is traditionally considered as the best method for generating signals of potential risk associated with pharmacological treatments. This approach usually allows early identification of safety problems associated with drugs and enables health authorities to issue regulatory measures to prevent the harm to many patients as much as possible. However, there are some fields of medicine in which the efficiency of spontaneous reporting in the assessment of drug safety is debated or should be integrated with different approaches. One of these fields is oncology. Pharmacovigilance dedicated to detection of ADRs associated with antineoplastic agents in cancer patients requires frequent updates, since oncology is one of the medical fields with the most active research and development of new drugs. These drugs are often "first in class drugs", acting on molecular receptors never targeted before, for which ~~the~~ limited knowledge exists. Therefore particular caution in the safety monitoring of these medicinal products is required. Furthermore, the "biotechnological" revolution of pharmacological therapies involved widely oncologic drugs, with several monoclonal antibodies approved for clinical use being indicated for treatment of cancers in different tissues. It would be important to verify whether traditional methods employed for signal detection through the evaluation of datasets of spontaneously reported ADRs, can be applied to this "superclass" of drugs, or a different approach could be considered.

Seruga and coworkers [1] compared the updated drug labels with the respective drug labels published after first approval of 12 anticancer target agents to assess the number of clinically relevant ADRs identified in the post-marketing period. This study was able to identify 76 serious ADRs reported in updated drug labels, and 50% (n = 38) were potentially fatal. Of these, 49% and 58%, respectively, were not described in initial drug labels. After a median of 4.3 years between initial approval and update of drug labels, 42% (n = 5) of targeted cancer agents received one or more boxed warnings [1]. Although this circumstance can be in part due to a delay in the update of drug labels, particularly for those approved with accelerated procedures [2], these results demonstrated the need for an accurate ADR reporting after approval to reduce the time of identification of relevant safety issues associated with oncologic drugs. Another study showed that potentially fatal ADRs to oncologic drugs may be identified as many as 36 years after a drug received marketing authorization (e.g. thioguanine-associated bone-marrow depression in genetically susceptible patients). Although this delay could be due to "primitive" methods of assessment and not adequate Pharmacovigilance systems (thioguanine was approved in 1965), and fortunately the time was reasonably reduced at present [3], it is conceivable that an under-reporting

contribute at least in part to prolong the time of ADR identification. Under-reporting is a common problem in Pharmacovigilance and it is likely to be higher for oncologic drugs. The perception of risk/benefit of a treatment by physicians is usually conditioned by the clinical severity and prognosis of the disease to be treated. On this basis, ADRs involving oncologic drugs may be sometimes regarded as a secondary problem, and their spontaneous reporting is usually considered as a low-priority activity in the daily life clinical practice. Since cancer patients are usually quite ill and the antineoplastic agents used are often quite toxic, the threshold for spontaneous ADR reporting is unfortunately fairly high. Their reasoning for reporting only very severe and unusual suspected ADRs is that their patients experience ADRs very frequently and some practical discretion must be used in reporting. Furthermore, it is conceivable that the oncologist tends to under-evaluate the importance of recording any adverse event that is not strictly related with the disease progression. Sometimes, identification of a causal relationship between an event and a treatment is not easy with such complex patients, and he may tend to ascribe the adverse event to another underlying non-cancer disease, therapy or cancer progression. Moreover, experience has shown that oncologists are more prone to report new ADRs to their peers (oncology meetings and journals) than to national spontaneous reporting systems. Finally, several toxicities associated with traditional anticancer drugs are frequent and expected (i.e. bone marrow depression, nausea, vomiting, alopecia), and the oncologist is well trained to recognize them and "preferentially" reporting these effects both in pre- and post-marketing phases of drug development. With regard for the above mentioned issues, the involvement of well-trained patients in ADR reporting using online tools would be an interesting approach to improve the efficiency of Pharmacovigilance of oncologic drugs. In this context, promising preliminary results have been obtained by the group coordinated by Basch at the Memorial Sloan-Kettering Cancer Center in New York [4, 5].

Besides underreporting, several authors have suggested plausible causes to explain the relatively high number of, at least initially, not well characterized clinically relevant ADRs associated with anticancer drugs, and the time required for their identification [6-8]. One of the major concerns appears to be the use of inadequate adverse event report form. Belknap and coworkers (2010) [7] noted that only a small number of items, considered as essential for the definition of an adverse events (4/34), is listed in the Institutional Review Board (IRB) report form used for clinical trials in 49 USA cancer centers. Furthermore, it is important to note that the amount and quality of information communicated to IRBs is not consistent with that contained in medical records [8]. It is conceivable that this will apply even to postmarketing reporting forms.

The second possible explanation is the high need for novel therapeutic options to treat cancer. The clinical relevance of the disease confers a high value to the benefit of new treatments and rises the

threshold of acceptability of safety problems. As a consequence, several regulatory authorities (including FDA) have accelerated the procedures for anticancer drug approval (median time save compared with regular approval: 3.9 years; range 0.8-12.6 years) [9] since the beginning of 90' [10], and this circumstance may theoretically result in the early release of unsafe or ineffective drugs. Therefore, a higher number of unknown ADRs may be uncovered, in comparison with drugs belonging to other classes.

Third, it is important to note that the population exposed to anticancer drugs during pre-marketing studies is quite different, as compared to that receiving the drug in the post-marketing phase. The benefit/risk balance changes from early-in-human trials to the population treated after the product is authorised. Indeed, patients included in first-in-human trials have often exhausted all standard treatments and have complicated medical histories (usually an average of at least 5 prior lines of treatments in phase 1). Early phases clinical trials represent the last hope for the majority of patients or even a way to benefit future generations. Unmet medical needs or the lack of other treatment options can sometimes be the main benefit for patients. After approval, new anticancer treatments enter a process of continue investigations that, in case of favorable outcomes, progressively turn them into first line therapies intended for patients who are relatively healthier and hold longer survival expectations, as compared to those of clinical trials. Therefore, long term safety, which is not regarded as an important issue in end-stage patients during early clinical trials, may become a matter of concern in daily-life clinical practice in "healthier" subjects.

On this ground, it is important to consider reporting of adverse reactions to anticancer drugs as an important tool for generating signals of risk to be investigated in further studies. Nevertheless, the nature of these drugs and the peculiarities of oncologic patients require particular caution in the assessment of causality and identification of the risk during the post-marketing experience. This review is aimed at collecting the available studies performed on databases or datasets of spontaneously reported adverse reactions to oncologic drugs to assess what kind of information can be retrieved using these source of data. The methodologies of selected studies will be evaluated to highlight limitations and strengths with a particular focus on those that can be peculiar of the oncologic setting.

Methods

A literature search was performed using PubMed/MEDLINE and EMBASE up to December 2013 without language restrictions. The key search terms for identifying investigations on spontaneous ADR reporting databases were: "spontaneous ADR reporting" or "pharmacovigilance" or "post-

marketing surveillance" or "signal detection" or "disproportion analysis". The following keywords, related to oncologic drugs, were selected: "oncologic drugs", "anticancer drugs", "cancer", "target therapies", "monoclonal antibodies", "aromatase inhibitors", "alkylating agents", "taxanes", "antimetabolites", "tyrosine-kinase inhibitors", "anti-estrogen drugs", "antracyclines", "platinum derivatives", "vinca alkaloids". The studies included in the present article were those focused on any anticancer pharmacological treatment, and performed using, at least in part, data retrieved from spontaneous ADR reporting databases. Studies on anticancer agents used with indications other than cancer treatment or in which the indications were not clearly stated, were excluded from the analysis. Each title and abstract was reviewed in order to determine whether the paper was relevant to the review topic. For all potentially eligible references, the full-text was obtained and the studies were included if they met the pre-specified inclusion criteria. The reference lists of retrieved articles were also reviewed for identifying additional relevant studies. Black box warning have been included only when included in the reference list of selected articles.

Based on methodological approaches, studies were classified as qualitative, quantitative or both. The qualitative approach was defined by case by case analysis of demographic and clinical data. The quantitative approach refers to the application of data mining algorithms to the drug-event pairs recorded in the database to identify disproportions [11]. Disproportionality analysis measures are built up to identify combinations of drug exposures and ADRs that occur disproportionately often, as compared to other drug-event combinations. Several different disproportionality measures have been proposed in the literature [12-14], which can generally be divided into two categories: frequentistic and Bayesian. The most popular frequentistic methods include the proportional reporting rate (PRR) [15] and the reporting odds ratio (ROR) [16]. Among the Bayesian approaches, the Bayesian Confidence Propagation Neural Network (BCPNN), which estimates the information component (IC) [16], the Multi-item Gamma-Poisson Shrinker (MGPS) [17, 18], and the Empirical Bayes Geometric Mean (EBGM) [16] are the most prominent and widely used techniques. For each study, we tried to assess the rationale underlying the most frequent applications of analysis of spontaneous reporting databases in the assessment of safety of oncologic drugs.

Results

Upon application of the inclusion criteria, we were able to identify 27 studies that have attempted safety assessments of oncologic drugs by analyzing spontaneous ADR databases (Table 1) [6, 19-44]. The majority of these studies (n = 24) [6, 19-22, 24, 26-38, 41-44] were performed on the Food and Drug Administration (FDA) Adverse Events Reporting System (AERS). Nine studies

integrated spontaneous reporting data with literature data [6, 22-24, 27, 33-34, 44] and 2 studies included original data [33, 37]. Three studies used prescription data as denominator to estimate the incidence of reports [19, 20, 28]. Investigations were designed with several aims, most frequently to assess the relationship between a specific drug and a specific adverse event (n = 7) [22, 24, 26-28, 35, 42], but also for assessing the association between a specific drug with a class of reactions (n=5) [19, 23, 36, 37, 40], as well as drug classes with a specific reaction (n=2) [6, 33], and drug classes with a class of reactions (n=4) [29, 34, 39, 43]. When the methodological approach was considered (Table 2), 12 studies [19, 20, 22-24, 27, 33, 36, 37, 39, 40, 42] were performed with a qualitative approach, 9 with a quantitative [21, 29-32, 38, 41, 43, 44], and 6 with an integrated approach (both quantitative and qualitative) [6, 25, 26, 28, 34, 35]. Fifteen studies [6, 21-23, 25, 27, 29-32, 34-37, 40] investigated labeled ADRs, while 6 studies [19, 24, 26, 28, 33, 42] analyzed data from few cases identified by pre-marketing studies or spontaneous reporting. Five studies were conducted to identify unexpected ADRs [20, 38, 39, 43, 44]. The last study investigated all drugs (including anticancer drugs) with a significant disproportional reporting pathway for a specific ADR (pneumothorax) [41].

Expert commentary & five-year view

The main purpose of collecting spontaneous ADR reports is the early identification of clues of potential toxicities associated with drug treatments that are novel by virtue of their nature, severity or frequency [11]. Before powerful computer technology was available, this process, called "signal detection analysis" relied solely on case-by-case study, implying that each individual case report of a suspected ADR submitted to a spontaneous reporting system was reviewed by an experienced assessor, who evaluated the likelihood that a clinical picture was caused by the drug and checked for unusual clinical elements within the case. Despite this "qualitative" approach has proven its efficacy, the growing availability of data and the increase in the complexity of treatment-event associations (i.e. multifactorial evaluations, such as drug-drug interactions or syndromes) have required the development of "quantitative" approaches. The latter are based on the identification, within the database, of an unexpected higher frequency of a given suspected drug-adverse event association, as compared to a null or a control value (usually the frequency of the same adverse event estimated for all drugs within the database) [14, 16, 18]. Reporting frequency in excess of chance expectation is one of the several possible indicators of a previously unrecognized association with significance for patient safety. Nevertheless, the identification of a disproportion in a database of spontaneous reporting does not necessarily imply a real risk, but rather a trend of abnormal signaling that might be caused by several factors, other than the specific risk associated

with drug treatment. Therefore, a quantitative approach must be supported by a critical clinical review process for being considered as a "credible" signal, which can trigger formal studies (i.e. observational cohort or case-control studies) aimed at confirming and quantifying the actual risk [45]. Clearly, when analyzing potential signals of risk related to anticancer drugs, particular caution is needed both in the analysis and interpretation of the results. In theory, the most effective sequential approach to the analysis of spontaneous ADR reporting databases would be a "quantitative screening" with data mining algorithms, followed by a "qualitative" clinical assessment to substantiate any relevant "disproportion", and this rule should also apply to the pharmacovigilance of anticancer drugs.

Quantitative approach

The possibility of identifying a signal of risk potentially associated with a cancer therapy through a quantitative approach has been demonstrated by several studies (6, 21, 25, 26, 28-32, 34, 35, 38, 41, 43, 44]. In general, it has been shown that both the frequentistic and Bayesian approach display the same ability of detecting a signal of risk in the oncovigilance setting [21, 28-32, 35, 44], although there is little evidence that the Bayesian approach could allow an earlier detection of the problem, as compared with the frequentistic one [21]. However, some limitations in the application of these methods to oncologic drugs deserve to be highlighted.

Cardiovascular toxicity of cancer drugs currently represents a relevant issue, especially for the most innovative targeted therapies, since many of these drugs seem to be all characterized by a certain cardiovascular risk [46]. Moreover, new drugs ensure increased survival rates as compared to traditional chemotherapies, to such an extent that long-term toxicity, like the cardiovascular one, has become a primary issue in cancer patients. In this regard, the oncologists and cardiologists have recently joined in a society (International CardiOncology Society) to collaborate in recognizing and treating cardiovascular toxicity of anticancer drugs [47]. Current evidence seems to suggest that data mining algorithms may not be suitable tools for the identification of certain ADRs, particularly for adverse events that are frequent in the general population and are not commonly thought to be drug-induced, such as cardiovascular ADRs [48]. This could be particularly true in the case of frail patients, such as cancer patients. Indeed, a cardiovascular event in a cancer patient will be more likely ascribed to co-morbidities or to age-related problems, and the probability of suspecting and reporting these events as drug-related is very low. For instance, in the study by Hauben et al.[21] data mining algorithms anticipated the detection of signals for almost all kinds of adverse reactions, with exception for cardiovascular events (namely thrombotic events associated with immunoglobulins).

The identification of cardiovascular ADRs in cancer patients is complicated not only by co-morbidities but even by concomitant treatments. Xu and Wang [43] attempted to identify "filters" to limit the problem of confoundings related to concomitant therapies. They artificially selected anticancer monotherapies (drug-event pairs apparently not considering whether the drug was suspected or concomitant) in the FDA AERS database and excluded all polytherapies calculating disproportion for monotherapies only for cardiovascular events. The result was a large number of highlighted disproportion on signals (n=320) with an elevated percentage of unexpected drug-event pairs (80.6%). It is reasonable to assume that only a small number of reports included in this analysis was a true monotherapy: in our experience, when an ADR report identified a single cancer drug, in most cases information related to concurrent treatments were omitted. Therefore, the application of this filter completely overlooks the problem of data quality, that is typical of all spontaneous reporting databases (the study by Shamloo et al. [38] revealed that in the AERS database the frequency of lack of essential information such as "gender" is high). Based on the above mentioned limitations, we believe that at present the most effective way for monitoring the cardiovascular safety of anticancer drugs is the use of drug- or disease-based registries [49-51]. Another approach that seems to be promising, especially to exceed the limited effectiveness of spontaneous reporting systems in generating signals of potential association between drugs and events, that can be common in frail patients, is the data-mining of medical records originated by the combination of multiple healthcare databases available in US [52]. Unfortunately, current experience with these methods, particularly in the setting of oncologic drugs, is limited and definite conclusions on the efficiency of these approaches can not be drawn yet.

Other kinds of ADRs, for which the identification of a disproportion could be difficult with data mining algorithms in cancer patients, could be neuropsychiatric events. For example, the study by Hauben et al. [21] demonstrated a certain limitation in the efficiency by which both the frequentistic and Bayesian approach allowed the early identification of neuropsychiatric events associated with interferons, as compared to ADRs belonging to different system organ classes. A couple of hypotheses can be made to explain these limitations: the first refers to the high prevalence (25-30%) of psychiatric conditions (mainly anxiety, stress-related diseases, and depression) in cancer patients [53]; caregivers likely consider these symptoms as disease-related, sometimes even as a part of a paraneoplastic syndrome (i.e. cerebral or meningeal metastasis), and therefore they rarely suspect and report a drug-related condition (high underreporting); the second is that psychiatric ADRs are commonly reported for other drugs [54]. Therefore, since the frequency of psychiatric ADR reports in the whole database is usually used as control, it is conceivable that the signal would be diluted and the evidence of disproportion might not emerge.

The problem of confounding by indication is without doubt one of the hardest to exceed. In several situations, it might identify disproportions within the database that are specifically related to the disease (e.g. paraneoplastic syndromes) rather than to treatment. In theory, we may agree with the use of a control as the expected frequency of an event not in the overall database, but in the whole class of anticancer drugs or, even better, in the group of drugs used for the same oncologic indication. However, this strategy would be rather difficult to pursue for several reasons, including for example the fact that very often a patient with a specific tumor is exposed both to the drug of interest and to the treatments used as controls. Therefore, the attempt of comparing ADR reports associated with a new oncologic drug A with reports on a traditional drug B (employed for the same indication, but not reporting drug A either as suspected or concomitant role) can lead to the selection of a cohort of control reports that is "historical" and does not contain information on the exposure to the new drug A merely because this drug was not available (or was not a first choice treatment) when the ADR related to control drug B was reported [55]. The use of a historical control cohort is associated with important biases, such as notoriety bias, or even biases stemming from different quality of care (e.g. different clinicians with different clinical approaches working in the same department in two different periods). An interesting idea to resolve the problem is to adjust the measure of disproportion using a parameter that takes into account the disproportion between the drug and the event [41]. This approach has proven to be effective in controlling the confoundings by indication for the majority of tests, and it is a promising tool for improving quantitative signal detection in the pharmacovigilance of anticancer drugs.

The reporting timeframe deserves much caution, particularly when the comparison is made among drugs approved in different periods. For example, in the study by Sakaeda et al. [30] three platinum derivatives were compared using data recorded in AERS in the period 2004-2009. There was apparently no reason for selecting this period instead of a different one. This study identified a significantly higher frequency of reports for several ADRs by cisplatin than by oxaliplatin or carboplatin. However, the timeframe did not consider that the three drugs were on the market for different periods. Indeed, in the early phase of marketing the number of spontaneous ADR reports is maximum (Weber effect) [56]. For this reason, in the above mentioned analysis [30], several ADRs could have been less reported for the oldest platinum compound, as compared with the newest, simply because "well expected" by the oncologist and, as such, not worthy of being reported. Moreover, the trend of use of anticancer drugs is varies considerably over time due to the high level of research and development activity in this field, as compared to that of other areas in medicine: with the introduction of a new drug, new treatment protocols gain diffusion, while old protocols decline (i.e. first choice drugs become second lines) and these circumstances may have great

influence on the trends of spontaneous ADR reporting. The differences observed in the above mentioned study [29] and in others [28, 30, 31] likely depend on the period selected for the analysis more than on actual differences in the safety profile. For this reason, we recommend caution when selecting the timeframe for the analysis.

The last "quantitative" issue is specific for biothecnological drugs. In a recent study performed on the World Health Organization database it has been confirmed that the pattern of spontaneous reporting of ADRs for biotechnological drugs differs from that of traditional ones [57]. The reason for this is probably the fact that, at present, the majority of these drugs are used to treat a limited number of severe conditions, mainly cancers and autoimmune diseases. Therefore, we have a selection of ADRs that is of course typical of these drugs, but it is even influenced by the features of the diseases for which these drugs are employed. Regardless of whatever the reason, the problem is that several methods of disproportion analyses (both frequentistic and Bayesian) are based on the identification of a frequency of ADR reporting, that differs from one established a priori, which is usually that expected for all the drugs in the database. Our doubt is whether it is correct to include all drugs in this "denominator" since the two "superclasses" of drugs (biotechnological drugs and traditional ones) present different reporting profiles. Studies aimed at verify this hypothesis are currently warranted.

Qualitative approach

Qualitative approaches have been applied to the identification of safety concerns for anticancer drugs in several studies [19, 20, 22-24, 27, 33, 36, 37, 39, 42]. These studies usually consist of case series with a number of cases that is relatively small (depends on the frequency of the adverse event of interest), and provide general overviews that are very detailed from a clinical stand point. Although it would be methodologically appropriate that these studies originate from disproportion signals identified by data mining algorithms, in several analysis, performed on anticancer drugs, these evaluations were based on initial observations of individual cases or groups of cases highlighted in the literature or by the regulatory agencies. The main limitations seems to be the incapability of anticipating, with the exception of rare occasions, the identification of new and unexpected signals of risk. However, they have several advantages, especially if developed with a strict methodology. In this regard, when dealing with anticancer drugs, it is appropriate to cite the example of the Research on Adverse Drug Events and Report (RADAR) network that has developed a dedicated survey protocol [26].

The RADAR project consists of a network of experts from different areas, with a specific focus on the field of oncology, which makes the system particularly reliable for investigating the safety of

oncologic drugs. The most important rationale underlying the development of this network relies on the evidence that safety data are effectively disseminated not only in national databases of spontaneous reporting but also in literature, databases of pharmaceutical companies and records of the different clinical centers contributing to the RADAR network. This implies that, in some cases, data mining algorithms might not identify a signal because the disproportion is estimated only in spontaneous reporting databases, thus neglecting useful data retrievable from other sources. In this situation, a qualitative approach might be more effective, particularly in the field of oncology, where underreporting is a more relevant problem as compared with other fields of medicine. In addition, the quality of data contained in databases of spontaneous reporting may be insufficient to effectively track the clinical characteristics (time to onset, more frequent symptoms, etc.) of an ADR. The integrated approach, based mainly on literature data, allows high accuracy in details, and therefore it has been used in several studies selected in the present review [6, 22-24, 27, 33, 34, 44]. The study by Evens et al. [35] showed a huge difference in the quality of data from literature (i.e. completeness), with respect to that of databases of spontaneous ADR reporting. For these reasons, the integrated approach, based on literature data for investigations in the pharmacovigilance of anticancer drugs, can be strongly recommended. Notably, in 2010 the RADAR network "evolved" into the Southern Network on Adverse Reactions (SONAR) project, maintaining this integrated approach to drug safety assessment, widening the network and implementing the variety of publications produced [58].

Overall, the quality of data recorded in databases of spontaneous ADR reporting largely depends on the forms used for reporting. The complexity of causality and clinical assessment of an ADR to anticancer drugs requires the collection of a large amount of variables that are essential not only for the evaluation of a single case, but even for the analysis of large databases on a population basis [7]. It is unlikely that all these information can be retrieved when ADRs are reported using standard forms (e.g. yellow card) provided by Regulatory Authorities. This point has been demonstrated, for instance, for ADRs reports on oncologic drugs to International Review Boards [8], but can likely be applied also to post-marketing ADR reporting forms. Standard ADR reporting forms have been developed to allow a simple interface and make easier the report by caregivers, thus saving as much as possible the few time they can spend for pharmacovigilance. Unfortunately, this strategy is not adequate in the oncologic setting. For this reason, some authors remark the higher value of published case reports, in which the narrative structure allows the inclusion of more details [59, 60]. In agreement with this consideration, in our opinion the collection of follow up information in a narrative structure can be recommended, especially when the adverse reaction reported for the oncologic drug is particularly relevant from a clinical point of view or is unexpected. Tools for free-

text data extraction can optimize the activity of data codification, which would pertain not to the onocologist but to the expert of pharmacovigilance.

Among the strengths of the RADAR (and SONAR) network, we consider as particularly remarkable that its protocol is based on two key elements. The first considers the clinical relevance of the event associated with the treatment and represents the start of a survey. The second takes into account the biological plausibility of the drug-event association of interest when assessing causality between drug exposure and event occurrence [61]. Several algorithms or criteria have been proposed to assess the degree of probability that an adverse event can be ascribed to a drug exposure. These tools have been created substantially on the basis of the criteria proposed by Irey [62] and Karch and Lasagna [63]: plausible temporal relationship between drug intake and the onset of symptoms; lack of alternative causes; positive response to drug dechallenge and drug rechallenge. When applied to oncologic drugs and to their peculiar adverse reactions these criteria must be verified with caution.

When assessing causality, a temporal relationship between drug intake and the onset of an adverse event is "plausible" when this time is compatible with the supposed pharmacological and biological mechanism underlying the event. This means that as much as possible efforts must be done to unravel the mechanisms of adverse reactions that are still unknown or only hypothetic in nature. Case reports and case series can be helpful to identify a temporal window from the first drug intake to the diagnosis of the event that can be considered as plausible, when the pharmacological mechanism is uncertain. Since dechallenge and rechallenge information are usually difficult to be evaluated or the information these items provide are of limited utility to support the evidence of a causal association, the identification of a plausible pharmacologic mechanism is likely the key element of causality assessment for oncologic drugs, or at least more relevant than for the majority of other drug classes.

The utility of dechallenge and rechallenge information for assessing causality depends on the nature of the adverse reaction. Many oncologic drugs are endowed with tumorigenic or other long-term effects for which dechallenge and rechallenge criteria can not be applied or do not provide any evidence of causality. On the other hand, since the administration of anticancer drugs is usually scheduled as cyclic administrations (usually once every three weeks), dechallenge and rechallenge information are often available for acute and often severe reactions (e.g. bone marrow depression, vomiting, diarrhea).

Ruling out alternative causes likely remains the main issue for causality assessment of adverse reactions to oncologic drugs. Indeed, the oncologic patient usually undergoes multiple drug exposures either concomitantly or sequentially over time. Oncologic drugs are seldom used as

monotherapies with the aim of avoiding tumor resistance. Therefore, it is quite hard to discriminate among the different oncologic drugs (and theoretically also those drugs given as supportive care to manage adverse events, such as corticosteroids or antiemetics) included in a treatment regimen, especially for adverse reactions shared by different classes of anticancer drugs (i.e. bone marrow toxicity, neuropathies). When considering medium or long-term effects, such as some infections and tumours, the contribution of previous lines of treatment (chemotherapy, surgery, radiotherapy) can never be ruled out. Furthermore, patients usually present important co-morbidities (e.g. cardiovascular disturbances), that must be considered, if not as potential causes, at list as risk factors for the occurrence of an adverse event. Finally, when a severe adverse reaction occurs, the dose of one or more drugs scheduled in the treatment regimen is usually reduced in the next cycle or the next cycle is skipped, and therefore drug exposure may be not regular over-time.

In conclusion, the evaluation of spontaneous ADRs for oncologic drugs by means of data mining algorithms is feasible and useful for the periodic screening of the safety profile of a treatment regimen, although the poor quality of data recorded in these databases may greatly affect the findings. Cardiovascular adverse reactions to oncologic drugs deserve particular attention and their monitoring currently seems more reliable with drug- or disease-based registries. The qualitative "validation" of disproportion signals identified with these algorithms is highly relevant and particularly challenging. A qualitative approach can be used not only as a validation strategy, but even as a signal detection, mainly when information are retrieved from different and heterogeneous sources. The FDA AERS was the main database used in currently available studies, and it would be interesting in the future to test the validity of these methods with other databases that are not currently open access (WHO, Eudravigilance), and to compare the results among different databases. Strategies aimed at improving the quality of data recorded in spontaneous ADR reporting databases for anticancer drugs should be developed and could include the development of ADR reporting forms dedicated to oncologic treatments. In the meantime, the use of literature data to integrate information obtained with spontaneous ADR reporting systems is recommended.

Key issues

- Oncology represents a field of medicine with a very active research and development of new drugs. The need for new medical tools against cancer has progressively reduced the time required by regulatory authorities for new drug approval. On the other hand, the newest drugs often improve the survival of cancer patients to such an extent that adverse effects

associated with long-term use must be considered more than in the past. As a consequence, the safety profile of anticancer drugs can be incomplete, when they receive marketing authorization and a close monitoring is required.

- Standard signal detection tools can be applied with caution to identify unexpected safety issues associated with anticancer drugs, due to the complexity of multi-drug treatments and the presence of comorbidities.

- Quantitative approaches, based on data mining algorithms, have proven to be valuable screening tools for the identification of potential new adverse reactions to oncologic drugs, but integrated qualitative approaches is recommended. Qualitative approaches can be regarded as the primary investigative strategies in some circumstances.

- Cardiovascular safety is a primary issue for several new anticancer treatments. Traditional tools for signal detection are likely not suitable for assessing cardiovascular safety. Drug- or disease-based registries are more effective for monitoring the cardiovascular toxicity of anticancer drugs.

- Causality assessment is complicated by patients frailty as well as by the complexity of treatments. Standard ADR reporting forms may be insufficient for collecting of relevant data, while published case reports represent more complete sources of information. Biological plausibility play a prominent role in the assessment of causality.

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Table 1. Studies on spontaneous ADR reporting databases involving anticancer drugs

Study	Main data sources (period)	Safety issue	Number of cases	Main results
Wysowski et al.1996 [19]	AERS (FDA) (1989 -1994) Prescription records	Flutamide - hepatotoxicity	46	Death (n=20) Median age 71 (range 47-85) Time to events onset: 5-270 days Hospitalized (n=26) Median age 69 (range 52-81) Time to events onset: 14-300 days Reporting rate (n=46): 2.5 per 100,000 prescriptions
Bennett et al. 2002 [20]	AERS (FDA) (1998-2000) Prescription records	NSA - interstitial pneumonitis	12 (bicalutamide) 16 (flutamide)	Case definition: dyspnea, new pulmonary infiltrates, no evidence of infection Positive rechallenge: 6 patients Positive rechallenge with a different NSA: 2 patients Bicalutamide Demographic: median age 73.5 (59-91) Outcome: death (3) Incidence: 0.01%[a] Flutamide Demographic: median age 75 (65-84) Outcome: death (7) Incidence: 0.04%[a]
Hauben et al. 2004 [21]	AERS (FDA) (up to 2003)	Oncology drugs - potentially fatal reactions	26 DEC	PRR or MGPS generated a signal for 24 of 26 DECs for selected cancer drugs. For 16 DECs the signal was generated well in advance (≥2 years) than standard approaches.
Bennett et al. 2006 [22]	AERS (FDA) (1998-2006) Lit (1998-2006)	Thalidomide - VTE Lenalidomide - VTE	1,118 (thalidomide) 8 (lenalidomide)	No demographic information from the AERS database provided in the article. 254 (23%) thalidomide-associated VTE patients received anticoagulant therapy. 6 (75%) lenalidomide-associated VTE patients received anticoagulant therapy. VTE rates from the analysis of phase II and phase III clinical trials on thalidomide (VTE cases: 585, 12%) and lenalidomide (VTE cases: 110, 8%).
Belknap et al. 2006 [23]	AERS (FDA) (1997-2003) Lit (1997-2004)	Gemcitabine - lung injury	178 (55 CT, 92 SR, 31 Lit)	Demographics: male 32% Seriousness: hospitalization (32%), death (37%) Cancer: lung (52%), pancreas (16%), breast (6%) Clinical features: dyspnea (70%), fever (35%), pulmonary infiltrate (22%), cough (19%) Median time to ADR identification: 48 days (range 1-529) Frequently co-administered drugs: paclitaxel (13%), docetaxel (13%) Estimated frequency: > 10% (317 patients with lung injury from 11 phase II-III clinical trials)

Study	Main data sources (period)	Safety issue	Number of cases	Main results
McKoy et al. 2007 [24]	AERS (FDA) (2000-2004) Lit (2000-2005) FDA mandatory registry	Gemtuzumab - SOS	104	Demographic: 99 adults, 6 pediatrics Outcomes: hospitalization (80%), death (60%) Signs and symptoms: hyperbilirubinemia, painful hepatomegaly, ascites, and sudden weight gain Time to symptom development: 10-13 days following gemtuzumab administration SOS incidence (clinical trials): 3% (low dose monotherapy or + non-hepatotoxic agents); 28% (gemtuzumab + thioguanine); 15% (high dose monotherapy). SOS incidence (FDA registry): 14% (SCT); 9% (non-SCT)

Gonzalez et al. 2008 [25]	SPD (1999-2006)	rituximab - ADRs trastuzumab - ADRs	69 (rituximab) 23 (trastuzumab)	Rituximab
				    Demographics: male: 53.6%; mean age: 54.9 ± 2.0
				    Cancer: lymphoma 62.3%, unknown 27.5%
				    Main ADRs: white cell disorders (n=18; ROR: 22.2; 95%CI: 12.9–38.2), other suspected drugs in 14 cases
				    Mean time to ADR identification: 20.9 ± 7.8 days
				Trastuzumab
				    Demographics: female: 91.3; mean age: 55.5 ± 2.6
				    Cancer: breast: 60.8%, unknown: 13%
				    Main ADRs: cardiac failure (n=7, ROR: NA), other suspected drugs in 5 cases
				    Mean time to ADR identification: 13.7 ± 5.7 days

McKoy et al. 2008 [26]	AERS (FDA) (NA)	Bevacizumab - diverticulitis	11	PRR: not significant Estimated rate in a clinical trial on bevacizumab + carboplatin and pemetrexed 11% (n=4)
Carson et al. 2009 [27]	AERS (FDA) (1997-2008) Lit (1997-2008)	Rituximab - PML	52 (LD) 5 (not LD)	Demographics: male 43.8%; median age: 62 years (range 30-89) Survival: 10% Cancer: CLL (24.6%); FL (19.3%), NHL (17.5%) Clinical features: confusion, mental alterations (54.4%), focal motor weakness, hemiparesis (33.3%) Median time to ADR identification: 5.5 months Frequently co-administered drugs: corticosteroids (78.9%), CyPh (73.7; Vinca alkaloids (57.9%)
Yang et al. 2009 [28]	AERS (FDA) (2005-2007) Prescription records	Lenalidomide - VTE	41	Exposed patients (USA): 7764 patients (RevAssist data, company's proprietary restrictive distribution program) VTE reporting rate of 0.53% MGPS, PRR, ROR: not significant for lenalidomide-VTE but significant for lenalidomide+ESAs+VTE

Study	Main data sources (period)	Safety issue	Number of cases	Main results
Sakaeda et al. 2011A [29]	AERS (FDA) (2004-2009)	Platinum agent - hypersensitivity reactions	72 (cisplatin) 313 (carboplatin) 196 (oxaliplatin)	No demographic or clinical details provided PRR, ROR, IC and EBGM: signal substantially confirmed for carboplatin and oxaliplatin but not for cisplatin. Bevacizumab co-administration affect the reporting of severe oxalipatin hypersensititvity reactions.
Sakaeda et al., 2011B [30]	AERS (FDA) (2004-2009)	Platinum agent - ADRs	28,382 (cisplatin) 24,835 (carboplatin) 21,168 (oxaliplatin)	No demographic or clinical details provided PRR, ROR, IC and EBGM: confirmed signals for all platinum compounds: nausea, vomiting, acute renal failure, neutropenia, thrombocytopenia, and peripheral sensory neuropathy. Signal of nausea and acute renal failure was stronger for cisplatin as compared with the other compounds. Signal of increase in blood level of creatinine not detected for carboplatin. Thrombocytopenia was reported more frequently for carboplatin. Reports of peripheral sensory neuropathy were significantly higher for oxaliplatin, and less common for cisplatin and carboplatin.
Kadoyama et al. 2011 [31]	AERS (FDA) (2004-2009)	Anticancer drugs - hypersensitivity reactions	319 (paclitaxel) 114 (docetaxel) 1 (procarbazine) 8 (asparaginase) 1 (teniposide) 59 (etoposide) 151 (doxorubicin) 30 (6-MP) 162 (5-FU) 170 (CyPh) 47 (cytarabine)	No demographic or clinical details provided PRR, ROR, IC and EBGM: signal confirmed (at least 1 of the 4 methods identified the signal) for mild sensitivity reactions associated with paclitaxel and 5-FU, severe sensitivity reactions with paclitaxel and lethal sensitivity reactions with paclitaxel, docetaxel and 5-FU.
Kadoyama et al. 2012 [32]	AERS (FDA) (2004-2009)	5-FU - ADRs Capecitabine - ADRs	40,284 (5-FU) 39,928 (capecitabine)	No demographic or clinical details provided PRR, ROR, IC and EBGM: signals of leukopenia, neutropenia, thrombocytopenia are stronger for 5-FU than for capecitabine, while signals of nausea, vomiting and hand-foot syndrome were stronger for capecitabine than for 5-FU.
Edwards et al. 2011 [33]	AERS (FDA) (1998-2008) Original data Lit (1998-2008)	Anticancer drugs - bone loss	228 (fractures)	Demographics: age distribution > 30 years (coincided with the age of breast cancer therapy) Fracture sites: ≤ 64 years of age: 78 fractures, 15 cases (19%) of hip and femur fractures. Suspected drugs: aromatase inhibitors (n=149, 65%)

Study	Main data sources (period)	Safety issue	Number of cases	Main results
Raisch et al. 2011 [34]	AERS (FDA) (up to 2009) Lit (up to 2009)	Taxanes - anaphylactic reactions	290 (docetaxel) 683 (paclitaxel)	Mortality: 54% (docetaxel) vs 29% (paclitaxel); p < 0.001 Mortality with PPMs administration: 54% (docetaxel) vs 29% (paclitaxel); p < 0.001 EBGM: 1.74 (docetaxel); 2.50 (paclitaxel)
Evens et al. 2011 [35]	AERS (FDA) (1999 -2009) Lit (1999 -2009)	Rituximab - HBV reactivation	183 (Lit) 118 (AERS)	Demographic: median age: 57.5 years (range 21-83): male 75; female 43 Outcomes: death 58.4% PRR: 28.5 (95% CI 23.9-34.1); EBGM: 26.4 (95% CI 21.4-31.1) Overall completeness ratio of literature vs AERS: 2.37 (p<0.0001)
Lee Villano et al. 2012 [36]	AERS (FDA) (1998 -2008)	Temozolamide - major hematological ADRs	112	Demographic: male 40% Cancer: CNS 76%, melanoma 3%, lymphoma 3%, brain metastasis 3% Major ADRs: AA (n=39); aplasia (n=37); leukemias (n=17); agranulocytosis (n=7); MDS (n=7); lymphoma (n=5) Age, outcomes, median duration of treatment, median onset symptoms were stratified by adverse event
Sarganas et al. 2012 [37]	AERS (FDA) (2007 -2010) Original data	Temozolamide - liver ADRs	154	No demographic, outcomes or exposure information Main ADRs: hepatic functional abnormalities (n=48); hepatotoxicity (n=21); hepatic enzyme increased (n=18)
Shamloo et al. 2012 [38]	AERS (FDA) (2004 - 2009)	Bevacizumab - ADRs	11,312	Demographic: females 46%, male 44.9% and unknown 9.1% Major represented age group 51-75 years (n=3984); reports with unknown age (51.1%) Outcomes: hospitalization 6,496; death 1,980 Concomitant drug: oxaliplatin 63% Novel and clinically relevant PTs 63(PRR≥2)
Edwards et al. 2013 [6]	AERS (FDA) (1998-2009) Lit (1998 -2009)	Bisphophonates[b] - acute kidney failure	480	Demographics: females 56%; mean age: 66±10 years Cancer: multiple myeloma (n = 220, 46%), breast cancer (n = 98, 20%), prostate cancer (n = 24, 5%) Drugs: zoledronic acid (n = 411, 87.5%), pamidronate (n = 8, 17%), alendronate (n = 36, 2%). Outcomes: hospitalization (n = 304, 63.3%); death (n = 68, 14%). PRR (zoledronic acid): 1.22 (95%CI: 1.13-1.32) PRR (pamidronate): 1.55 (95%CI: 1.25-165)
Faye et al. 2013 [39]	FPD (2008-2010)	Protein-kinase inhibitors - serious cutaneous reactions	94 (115 ADRs)	Demographics: male 63%; mean age: 62.6±15.4 years Cancer: liver (26 ADRs), lung (20), kidney (17), CML (12) Drugs: sorafenib (40%), erlotinib (25.2%), imatinib (13%), subitinib (13%) Seriousness: hospitalization (55%), death (2%) Clinical features: maculopapular rash (25.2%), hand-foot syndrome (15.7%), papulopustular rash (13.0%) (17% unlabelled)

Study	Main data sources (period)	Safety issue	Number of cases	Main results
Grandvuille min et al. 2013 [40]	FPD (1985-2010)	Cetuximab - infusion ADRs	374	Infusion ADRs more reported in head and neck than colorectal cancer ($p < 0.001$). Fatal infusion ADRs: 7 (5 occurred in head and neck cancer patients). Infusion ADRs were more likely to be severe during the first administration (OR = 7.40; 95%CI: 2.21-24.71)
Hauben et al. 2013 [41]	AERS (FDA) (1969 - 2010)	All drugs - pneumothorax	3681	For 26 oncology drugs most evident SDR-ADE Most evident SDR-ADE: carmustine (EBGM= 8.52), dacarbazine (EBGM=7.57); bleomicine (EBGM=6.52), gefinitinib (EBGM=6.5), docetaxel (EBGM=6.3) Confounding by indication may play a prominent role in reports of drug-associated pneumothorax
Letarte et al. 2013 [42]	AERS (FDA) (1997 - 2009)	Bevacizumab - CNS hemorrhage	154	Demographic: median age: 62 years; female 54% Cancer: colorectal (42%), primary glioma (13%), breast (10%) Death for CNS hemorrhage (33%) Concomitant myelosoppressive chemotherapy 54% Concomitant medications associated with bleeding 31%: heparin (n=16), NSAIDs (n=10), warfarin (n=9)
Xu and Wang. 2013 [43]	AERS (FDA) (2004 - 2012)	Target therapies - cardiovascular events	11,173 DEC	DEC considered true positive pairs (signals): 320 (PRR) DEC not included in AERS FDA labels: 258 (80.6%)
Rosen et al. 2014 [44]	AERS (FDA) (1968 - 2012) Lit (1968-2012)	Anticancer drugs - dermatologic adverse event	2,098 SJS 1,555 TEN	SDR (PRR, EBGM) for SJS: bendamustine SDR (PRR, EBGM) for TEN: bendamustine, fludarabine, procarbazine, busulfan, clorambucile, lomostine

5-FU: 5-fluorouracil, 6-MP: 6 mercaptopurine; AA: aplastic anaemia; ADR: adverse drug reaction; AERS: Adverse Events Reporting System; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CNS: central nervous system; CyPh: cyclophospamide; DEC: drug event combination; EBGM: empirical Bayes geometric mean; ESA: erythropoiesis-stimulating agents; FDA: Food and Drug Administration; FL: follicular lymphoma; FPD: French Pharmacovigilance Database; HBV: hepatitis B virus; IC: information component; Lit: medical literature; MDS: myelodysplastic syndrome; MGPS: multi-item gamma Poisson shrinker; NHL: non-Hodgkin lymphoma; NSA: non-sterodial anti-androgen; NSAIDs: non-steroidal antinflammatory drugs; ONJ: ostheonecrosis of the jaw; PPMs: prophylactic premedications; PML: progressive multifocal leukoencephalopathy; PRR: proportional reporting ratio; RADAR: research on adverse drug events and reports project, ROR: reporting odds ratio; SCT: stem cell transplantation; SDR: signal of disproportionate reporting; SJS: Stevens-Jhonson syndrome; SOS: sinusoidal obstructive syndrome; SPD: Spanish Pharmacovigilance Database; SR: spontaneous reporting; TEN: toxic epidermal necrolisis; VTE: venous thromboembolism
a: number of spontaneous reports over numbers of users provided by a drug-based registry; b: cancer indication

Table 2. Studies on spontaneous ADR reporting databases involving anticancer drugs: approach, evidence and rationale

Study	Approach	Evidence/Rationale
Wysowski et al.1996 [19]	Qualitative	Spontaneous reports and few cases in clinical trials
Bennett et al. 2002 [20]	Qualitative	ADR reports associated with other drugs belonging to the same pharmacological class
Hauben et al. 2004 [21]	Quantitative	Reactions labeled. Comparing the efficiency of several data mining algorithms
Bennett et al. 2006 [22]	Qualitative	Reactions labeled. General case review
Belknap et al. 2006 [23]	Qualitative	Reactions labeled. General case review
McKoy et al. 2007 [24]	Qualitative	Spontaneous reports and few cases in clinical trials /general case review
Gonzalez et al. 2008 [25]	Quantitative and qualitative	Reactions labeled. General case review
McKoy et al. 2008 [26]	Quantitative and qualitative	Spontaneous reports and few cases in clinical trials/general case review
Carson et al. 2009 [27]	Qualitative	Reactions labeled. General case review
Yang et al. 2009 [28]	Quantitative and qualitative	Spontaneous reports and few cases in clinical trials
Sakaeda et al. 2011A [29]	Quantitative	Reactions labeled. Disproportional analysis
Sakaeda et al. 2011B [30]	Quantitative	Reactions labeled. Comparison of ADR reporting profile among platinum-derivatives
Kadoyama et al. 2011 [31]	Quantitative	Reactions labeled. Comparison of hypersensibility ADR reporting profile among anticancer drugs.
Kadoyama et al. 2012 [32]	Quantitative	Reactions labeled. Comparison of ADR reporting profile between 5-FU and CAP
Edwards et al. 2011 [33]	Qualitative	Spontaneous reports and few cases in clinical trials /general survey
Raisch et al. 2011 [34]	Quantitative and qualitative	Reactions labeled. Disproportional analysis
Evens et al. 2011 [35]	Quantitative and qualitative	Reactions labeled. Disproportional analysis and general case review
Lee Villano et al. 2012 [36]	Qualitative	Reactions labeled. General case review
Sarganas et al. 2012 [37]	Qualitative	Reactions labeled. General case review
Shamloo et al. 2012 [38]	Quantitative	Disproportional analysis for the detection of unexpected ADRs
Edwards et al. 2013 [6]	Quantitative and qualitative	Reactions labeled. Disproportional analysis and general case review
Faye et al. 2013 [39]	Qualitative	Identification of unexpected ADRs for the class of protein kinase inhibitors
Grandvuillemin et al. 2013 [40]	Qualitative	Reactions labeled. General case review
Hauben et al. 2013 [41]	Quantitative	Identification of drugs with a disproportional reporting pathway for pneumothorax
Letarte et al. 2013 [42]	Qualitative	Few cases in clinical trials. General case review
Xu and Wang. 2013 [43]	Quantitative	Identification of unexpected cardiovascular ADRs
Rosen et al. 2014 [44]	Quantitative	Identification of unexpected serious dermatological ADRs
5-FU: 5-fluorouracil; ADR: adverse drug reaction; CAP: capecitabine		