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Market access and assessment of post-marketing use and cost of biological drugs in oncology

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Chapter 1: General introduction

1.1. Background

1.1.1. What is a biologic drug?

In the last years, the pharmaceutical market has undergone several important changes, including the development of biological drugs that have revolutionized the treatment of several diseases, particularly in the oncologic setting. The European Medicines Agency (EMA) defines a biological drug as "a biological medicinal product [that] contains one or more active principles derived from a biological source. Some of these active principles may already be present in the human organism, for example proteins such as insulin, the growth hormone and erythropoietin. Biological medicinal products are also larger and more complex molecules than non-biological medicinal products. Only living organisms are capable of reproducing such complexity" (European Medicine Agency, 2011).

It was in 1980 that biological drugs were introduced into the market and the number of these drugs has been growing ever since (Chirino et al, 2004). Biological drugs are produced by living cells and require advanced manufacturing and production processes. These drugs consist of large recombinant proteins that undergo complex post-translational modifications. Such complex molecules are typically expensive to develop and to produce on an industrial scale. In addition to the production method, this complexity can determine a degree of variability in the molecules of the same active ingredient, especially in the various batches of a drug (European Medicine Agency, 2011).

1.1.2. Biological drugs in clinical practice

Due to a remarkable specificity for biological targets and the positive results obtained in clinical practice, biological agents have greatly changed the course of clinical history in the treatment of chronic diseases (Matucci et al, 2016). These drugs are used in many therapeutic areas such as rheumatology, hematology, gastroenterology, dermatology and specially in oncology. Biological therapy for cancer is used in the treatment of many types of cancer to prevent or delay tumor growth and to prevent the spread of cancer, causing fewer toxic side effects than other cancer treatments.

Most of the recently marketed drugs in oncology are indeed biological drugs such as monoclonal antibodies which are considered to be highly innovative as they targeting specific receptors or differentiation markers over-expressed on tumor cells (Mach, 2012). They improved the management of specific types of cancer with substantial benefits in terms of disease progression and quality of life, improving progression free survival (Norum et al, 2011).

Biological drugs anti-tumor activity is carried out on molecular targets, which are molecules or receptors located within the cell and are involved in the growth, angiogenesis and cell proliferation. There are many advantages to use monoclonal antybodies (mAbs) in oncology, for example drugs such as trastuzumab for breast cancer and cetuximab for metastatic colorectal cancer. First and foremost, these drugs can cause a considerable enhancement for chemotherapy and conventional therapies. Secondly, because of their improved selectivity against cancer cells, mAbs cause less toxicity to healthy cells, although side effects directly associated with their use are present (Francescon et al, 2016).

Biological drugs are administered for tumor with high prevalence, such as breast cancer, colorectal cancer and lymphoma. Among the Italian women, the tumor most frequently diagnosed in the past was breast cancer with 692,955 women prevalent in 2015 followed by colorectal cancer (201,617 prevalent), thyroid (124,850) and uterine body (109,981). Among men, nearly 400,000 (398,708) were prevalent after a diagnosis of prostate cancer; 225,459 prevalent after a colorectal cancer diagnosis and 204,158 after diagnosis of bladder cancer (I numeri del cancro in italia, 2016).

1.1.3. Regulatory aspect of biologic drugs

Centralized procedure is necessary to entry market of all biological and biosimilar drugs, is mandatory in all its elements and consists of approval by the European Medicine Agency (EMA) in collaboration with the National Agencies and directly applicable in each member state. The request must be submitted to the European Medicines Agency (EMA) and the CHMP (Committee for medicinal products for human use) carries out the scientific evaluation for EMA (CHMP opinion). When the CHMP issues its assessment, the holder may submit the request to Regulatory Agencies to set the price and conditions for possible reimbursement. At the end of the procedure, if the benefit-risk assessment of the drug is positive, the European Commission grants an authorization that is valid for all EU countries. If the evaluation is negative, the authorization is refused and the rejection extends to all EU states. The reimbursement of the drug is always established by the regulatory agency of each state member.

1.1.4. Economic impact of biologic drugs

From 2006, EMA already authorized 21 new products with indications both in supportive therapy and chronic conditions and it has been estimated that by 2018 biological drugs will account for 49% of the entire pharmaceutical market**.** The expenditures generated by their use for National Health Service (NHS), today represent a problem that in the next years will be crammed by the introduction of biosimilar drugs in to the market in areas such as oncology, while in other therapeutic areas, for example rheumatology, dermatology and gastroenterology, they have already made their entry. The top 30 active ingredients represent 47.3% of the expenditure and mainly include active ingredients which fall under the category of antineoplastic agents. In 2016, between drugs used in hospital, the first three active principles with the expenditure more high are trastuzumab (222.7 million Euros), bevacizumab (189.6 million euro) and rituximab (156.3 million Euros) (Osmed, 2016). The expiry of patents for the first biological drug led to the development of biosimilar a biological medicine that is similar to another biological medicine that has already been authorized for use. For next years, with the entry into the market biosimilar drugs, there will be a significant reduction of pharmaceutical expenditure for the NHS and could allow the use of these innovative but expensive medicines to a wider population, especially for oncological patients. Following specific European guide lines, biosimilar drugs can be produced by other companies and sold at significantly lower prices, with a discount of around 20-30% (Francescon et al, 2016). In other European countries, for example in Norway, a discount of up to 89% is applied to biosimilar compared to the originator (Mack, 2015).

In February 2017, EMA approved biosimilar's rituximab (GABI Journal, 2017). Rituximab is a monoclonal antibody, anti CD20, used in the onco-hematological and in rheumatology area, is administered for high incidence pathologies such as chronic lymphatic leukemia and non Hodgkin lymphoma, and it's the first oncological biosimilar to receive regulatory agency approval internationally. In addition to rituximab, in the next few years, a number of biological drugs used for

cancer treatment will lose exclusivity, including trastuzumab, cetuximab and bevacizumab (Mcdonald et al, 2015). In September 2017, bevacizumab's biosimilar approved in America by FDA. In Europe, biosimilars are authorized through a centralized procedure too, which is valid for all member states, the differences remain with regard to market access, policy pricing, repayments and substitutability between biosimilar and originator (Buske et al, 2017.)

1.1.5 Research gaps in special populations: the pediatric setting

For particular population such as pediatric, the number of approved drugs is smaller than approved drugs for adult. Although in recent years the drugs approved for this population have doubled (Tomasi et al, 2017), the situation is not the same for approved pediatric drugs with oncology indication. The most common pathology is acute lymphoblastic leukemia but there are few studies and even less drugs approved for other oncological indications. It is important to investigate for these particular populations.

1.2. Aims

The aims of this thesis were: 1) to describe the regulatory pathways leading to drug approval at the regional level in terms of time to approval, number and type of drugs approved as well as economic impact, with emphasis on biological drugs; 2) to describe use and cost of biological drugs in oncology through real world data in a small catchment area in Southern of Italy; 3) to describe the state of the art concerning the research pipeline of biological oncologic drugs, with focus on pediatric indications.

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Chapter 2: Access to the market of medicines: Three Years' Experience of the Sicilian Regional Drug Formulary

Submitted to Health policy

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Abstract

Objective: To describe the approval timing and regional economic impact of the Sicilian Drug Formulary Committee approval process.

Data Sources: European public assessment reports, administrative acts published in the Italian government bulletin, Sicilian regional health department website, national electronic compendium, dossiers submitted to the Sicilian Drug Formulary Committee and Italian drug agency (AIFA) website were used.

Study Design: Newly approved drugs for which a dossier was presented to the Sicilian Drug Formulary Committee to authorize drug use in the Sicilian hospitals were identified from 1st January 2013 to 1st April 2016. The lag time between European Medicines Agency (EMA) and AIFA approval, and AIFA and Sicilian Drug Formulary Committee approval dates was calculated. The budget impact analysis (BIA) of approved drugs on the Sicilian region one year after their approval was performed.

Principal Findings: Median (IQR) lag time between EMA and AIFA approval and between AIFA and Sicilian Drug Formulary Committee approval was 15.1 (IQR: 10.9-21.5) and 3.6 months (IQR: 0.2-7.1), respectively. The BIA showed that all the drugs were associated with a total annual cost of € 525,489,586.

Conclusion: Drug approval lag times may lead to disparity in health services access. In Italy, this largely depends on national procedures.

Key words: Drug therapy access, budget impact analysis, drug approval time, health care services, drug release

Introduction

Drug marketing authorizations can be granted through different types of regulatory procedures in Europe: centralized, decentralized, mutual recognition and national procedures (Pammolli et al, 2009). The centralized procedure consists of approval by the European Medicine Agency (EMA) (European Medicines Agency 2017), followed by automatic approval at the European (EU) member state level. This is a mandatory procedure for all drugs derived from biotechnology processes including biosimilars, orphan drugs, anti-AIDS medicines, advanced therapies (such as gene-therapy, somatic cell-therapy or tissue-engineered medicines), antineoplastic drugs, anti-diabetics, drugs for the treatment of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and multiple sclerosis, autoimmune diseases and other immune dysfunctions and viral diseases. The mutual-recognition procedure occurs when a marketing authorization granted in one member state can be recognized in other EU member state. The decentralized procedure takes place when a medicine that has not yet been authorized in the EU can be simultaneously authorized in several EU member states (European Medicines Agency 2017).

The market access of drugs for use at the national and regional level is a long and complex process in Italy. The national procedure starts with an independent evaluation of a drug dossier presented by a pharmaceutical company (Minghetti et al, 2013). Irrespective of the approval procedure, drugs are initially granted a marketing authorization by the Italian Drug Agency (Agenzia Italiana del Farmaco, also known as AIFA) and are given a unique marketing authorization code known as an AIC code specific to the active ingredient, strength, formulation and marketing authorization holder (MAH). In addition, the drug price and type of reimbursement by the national healthcare system (NHS) are defined on the basis of an agreement between AIFA and the MAH. Drugs which can be covered by NHS are classified into three different categories in Italy: class A, H and C (*see Appendix SA1*), covering hospital/community pharmacies, hospital pharmacies and community pharmacies only respectively. This categorization allows for a therapeutic continuity of care between intensive and chronic/short-term therapies, in hospital or in the community respectively (Garattini et al, 2016).

After obtaining the marketing authorization at national level, Regional Drug Formulary Committees are in place in most Italian regions to evaluate and eventually approve drugs for regional hospital use, with the final goal of optimizing regional drug-related expenditure. In case of rejection of the drug approval at regional level, those drugs cannot be administered at hospital level neither can be prescribed by specialists working in public hospitals or ambulatories to out-patients. In Sicily, the Drug Formulary Committee (ProntuarioTerapeutico Ospedaliero Regionale Siciliano-PTORS committee) is composed of 21 members each having a different area of expertise, including oncologists, neurologists, internal medicine specialist, cardiologists, clinical pharmacologists, general practitioners, hospital pharmacists and regional public health officials. This panel of experts meets monthly to decide whether drugs should be included in the regional hospital formulary and to assess requests for post-marketing monitoring that are presented by MAHs using dedicated forms (*Figure 1*). The Sicilian Regional Drug Formulary Committee uses two different documents to take decision about drug approval/rejection (*see Table S2 in Appendix SA2*). The Sicilian Regional Drug Formulary Committee cannot include a drug in the regional formulary if it is not first included in the national pharmaceutical formulary. On the other hand, a drug may be excluded from the hospital formulary even if it has been granted a marketing authorization by AIFA at the national level. Consequently, a hospital cannot include a drug in its formulary if it is not first approved by the Sicilian Regional Drug Formulary Committee, which may also decide to restrict the regional use of drugs that

have been approved at AIFA only to highly qualified specialist centers. The decision on whether or not to include newly marketed drugs in the regional hospital formulary may be conditioned by the need for a cost containment strategy at a regional and local level. However, such strategies may impact the equality of treatment accessibility for Italian patients in different regions (Allegretti et al, 2004).

The latest data from the 2015 National Report on Medicine suse in Italy (Osservatorio Nazionale sull'Impiego dei Medicinali, OsMed) shows the dramatic impact of highly costly innovative drugs such as anti-hepatitis C drugs and anti-neoplastic drugs) on pharmaceutical expenditure in public hospitals. Over only two years (2013-2014), innovative medicines accounted for an additional increase of 23% (from 60.8% to 83.8%) of the total drug expenditure in Italian hospitals. In addition, almost all regions exceeded the hospital drug budget which was set at 3.5% of the total National Health expenditure, resulting in a total deficit of 1.5 billion Euros (Italian Medicines Agency 2015).

There is currently very little information on the length of the time needed to gain market access at the regional level in Italy once EMA/AIFA have approved newly licensed medicines, as well as the economic impact of regional approval of drugs in the hospital formulary. The aim of this study is therefore to describe the outcomes of the Sicilian Drug Formulary Committee in the years 2013-2016, by assessing the following issues: a) the number and types of drugs being approved or rejected; b) the lag time between the EMA/AIFA and Sicilian Regional Drug Formulary Committee approval, as an indicator of the speed of accessibility of newly marketed medicines at the Italian regional level; and c) the pharmaceutical budget impact analysis (BIA) on the regional healthcare expenditure after one year from the Regional Drug Formulary Committee approval.

Methods

Drugs of interest

From the 1st January 2013 to 1st April 2016, all the drugs for which a dossier was presented to the Sicilian Regional Drug Formulary Committee by an MAH were identified and classified into one of the following mutually exclusive categories: a) drugs requesting a new approval at the regional level; b) previously approved drugs at the regional level for which an extension of therapeutic indications was requested; c) drugs that were not approved by the Sicilian Regional Drug Formulary Committee. All drugs were classified and stratified by first level ATC (Anatomical Therapeutic Chemical) classification (available at: https://www.whoc.no/atc/structure_and_principles accessed 15thJuly, 2017). Assessment of the drug dossier by the Sicilian Regional Drug Formulary Committee is based on evaluation of drug-specific forms summarizing key information on clinical and economic aspects of the drug as compared to the available alternative options. Based on this information each individual member of the Committee fills an evaluation form concerning several parameters before each monthly meeting (*see Table S2 and S3 in Appendix SA2*). During the meeting consensus on the drug assessment from individual members is sought via discussion.

Source and type of information

Publicly available data sources were used to retrieve relevant information on drugs evaluated by Sicilian Regional Drug Formulary Committee as listed below:

- EMA,AIFA and Sicilian Regional Drug Formulary Committee marketing authorization/approval granting dates were obtained from European public assessment reports (authorization details), administrative acts published on the Italian government bulletin

(Gazzetta Ufficiale), and Sicilian regional department of health website, respectively(European Medicines Agency 2017;Sicilian Regional Health Authority 2017);

- Information on drug indication, innovative status and legal status (eligibility for repeat dispensing and allowed duration of repeat dispensing) was obtained from a national electronic drug compendium (i.e. Compendio Farmaceutico Ospedaliero – available at: https://www.farmadati.it/, accessed 15thJuly 2017) that contains information on drugs marketed in Italy;
- The presence of Managed Entry Agreements (MEAs), a system through which healthcare centers can be reimbursed for drug purchase costs by the drug manufacturer on the basis of their use in the hospital setting and achievement of certain outcomes after specific time period from drug treatment start. The reimbursement schemes for drugs are available on the AIFA website (available at:http://www.agenziafarmaco.gov.it/it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based, accessed 15thJuly 2017) and include, only for the drugs considered during the study period: *Cost Sharing*(price discount on the first therapy cycles for all patients eligible for the treatment), *Payment By Results* (full reimbursement from the manufacturer in case of therapeutic failure) and *Success Fee* (full reimbursement only for therapeutic success).
- The presence (if any) of a national drug monitoring registry was ascertained through AIFA website (available at http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottoposti-monitoraggio, accessed 15thJuly2017).The AIFA Monitoring registries system guarantees the appropriate use of drugs, drug safety post-marketing monitoring and outcome evaluation in relation to the managed entry agreement (e.g. payment by result at certain months after treatment start)(Montilla et al, 2015).

Regarding time to market access**,** the median number of months (along with interquartile range, IQR) elapsed between the EMA, AIFA and the Sicilian Regional Drug Formulary Committee approval dates were calculated as an indicator of the speed of the market access at regional level.

Budget impact analysis

The one-year pharmaceutical budget impact analysis (BIA) from a payer perspective (Sicilian Regional Healthcare System) was carried out on the basis of key epidemiological, clinical and economic data for 117 drugs that were newly approved by Sicilian Regional Drug Formulary Committee during the study period. For 29 of these drugs, it was not possible to calculate the BIA due to the lack of information on the estimated number of patients eligible for drug treatment. The BIA consisted of a stepwise process: first, we estimated the amount of active principle required by an average adult patient (we assumed an average body weight of 70 kg and an average body surface area surface area 1.8 m^2) for the main drug indication, in line with what is reported in the summary of product characteristics (SPC). Second, we calculated the total amount of active principle that was contained in an individual package (the highest price packages were considered) and quantified the number of drug packages needed to satisfy the patient's therapeutic needs during one-year treatment. The total drug purchase cost for one year of treatment of a single patient was hence calculated using ex-factory prices (i.e., the price paid out to the drug manufacturer).

Finally, the total annual cost per patient was multiplied by the total number of patients potentially eligible Sicilian for pharmacological treatment during first year in which the drug was included in the regional hospital formulary, as reported in the drug dossier (see *Appendix SA1*). If the recommended duration of therapy was not clearly specified in the SPC a one-year treatment regimen was assumed.

Results

From 1st January 2013 to 1st April 2016, the Sicilian Regional Drug Formulary Committee received the submission of 170 drug dossiers. Of these, 117 (68.8%) newly marketed drugs on the Italian market were approved, 29 (17.1%) drugs already available in the regional formulary received approval for a new therapeutic indication, while 24 (14.1%) were rejected. Of these 24 drugs, 14 drugs (58.0%) could be reimbursed by regional healthcare system through general practitioner (GP) prescription (i.e. reimbursement scheme class A), 5 (21.0%) could only be purchased out-of-pocket by citizens with a GP's prescription (i.e. reimbursement scheme class C), while 5 (21.0%) could not be prescribed by GPs at all as they were only for hospital use (i.e. reimbursement scheme class H).

Of the 117newly approved drugs, antineoplastic and immunomodulating agents (ATC L) were the largest group (N=37; 31.6%), followed by alimentary tract and metabolism drugs (ATC A; N=17; 14.2%), anti-infective agents for systemic use (ATC J; N=14; 12.0%) and nervous system drugs (ATC N; N= 12; 10.2%) (*Figure 2*).

*Figure 3*shows the time in months elapsed between EMA approval and AIFA approval and finally Sicilian Regional Drug Formulary Committee approval for each drug individually as well median time for drugs grouped at first level ATC.

The median lag time between EMA and AIFA and between AIFA and Sicilian Regional Drug Formulary Committee was 15.1 months (IQR: 10.9-21.5) and3.6 months (IQR: 0.2-7.1), respectively.

Regarding the types of reimbursement schemes for the approved drugs, several antineoplastic and immunomodulating agents(80.0%), anti-infectives for systemic use (57.1%) and alimentary tract and metabolism drugs (23.5%) belonged to class H (that, intended for exclusive use in the hospital), while several respiratory system drugs (88.9%), nervous system drugs (41.7%), and cardiovascular system drugs (33.3%) belonged to Class A, which are fully reimbursed by the NHS but purchased in an out-patient setting. Finally, alimentary tract and metabolism drugs (70.6%), cardiovascular system drugs (66.7%), blood and blood forming organs drugs (57.1%) and anti-infective drugs for systemic use (28.6%) were reimbursed by class A/PHT schemes (dispensed from the hospital pharmacy to out-patients (*Figure S1in Appendix SA2*).

Payment by Results, Cost Sharing and *Success Fees* were the most common MEAs for cost reimbursement of drugs belonging to ATC L (N=10, N=5, and N=1, respectively) (*Figure 4*).

Among approved 117 drugs, only18 (15.4%)were judged to be innovative by AIFA and therefore received fast track approval procedure. These innovative drugs belonged to ATC class L (N=9 out of 37 approved drugs having with ATC code L;24.3%), J (N=8 out of 14 approved drugs having with ATC code J; 57.1%) and M (N=1 out of 2 drugs having with ATC code M; 50.0%). Except for ATC Class D* and G* a mandatory drug monitoring registry was implemented upon AIFA request for at least one drug in all the other therapeutic classes and mostly for antineoplastic and immunomodulating drugs (N=30 out of 37 drugs with ATC code L; 81.1%), which had also the highest proportion of newly approved drugs for which the prescription was restricted to selected specialists' centers (N=25 out of 37 drugs with ATC code L; 67.6%) (*Figure S2 in Appendix SA2*).

Budget impact analysis

The budget impact analysis for all eligible patients showed that approved drugs were associated with a total estimated annual cost of € 525,489,586 payable by the regional healthcare system after the first year of approval, assuming that the indication of use was the primary indication and that the patient was an adult patient. *Figure 5*shows that the highest total expenditure is attributed to the ATC classes R, L and A.

Drugs having an ATC class R were associated with an estimated budget impact of € 209,897,637 for a total of 494,141 eligible Sicilian patients, making up 39.9 %of the total expenditure incurred by the regional healthcare system in Sicily. Drugs having ATC class L were associated with a similar expenditure (38.9 % of the regional healthcare expenditure), that is, € 204,308,945, despite the comparatively much lower estimated eligible population (N=7,028). The third ATC class with highest economic impact was ATC class A, which nevertheless only accounted for 7.2% of the regional healthcare budget, having an estimated cost of € 37,674,401 for a total of 68,360 Sicilian patients eligible for treatment. It was found that the budget impact of ATC class S was €968,801 for an estimated 48,327 eligible patients in Sicily, accounting for only 0.2%of the regional healthcare expenditure, that is, the lowest expenditure compared to other ATC classes of drugs approved for inclusion in the regional hospital formulary in the study period.

Discussion

To our knowledge, this is the first study which provided a comprehensive overview of the regulatory and economic outcomes of an Italian Regional Drug Formulary Committee with respect to newly approved drugs for hospital use.

Specifically, the activities of the Sicilian Regional Drug Formulary Committee during the years 2013-2016 was analyzed in detail. The general objective of this committee is to promote the judicious use of marketed drugs at the regional level while containing pharmaceutical expenditure. After obtaining the marketing authorization at the national level by AIFA, the Sicilian Regional Drug Formulary Committee, like all other Regional Drug Formulary Committees in Italy, can evaluate and eventually approve drugs for regional hospital use. When the regional committee rejects the request for the inclusion of a drug in the regional hospital formulary, if the drug belongs to class A, it can still be prescribed by a general practitioner in an out-patient setting but not by specialists working in public hospitals or ambulatories to outpatients. However, if a rejected drug belongs to class H (for in hospital use only), it cannot be prescribed at all at regional level. Almost all the drugs approved by AIFA were also approved by the Regional Drug Formulary Committee. In contrast, the majority of drugs not receiving approval could be prescribed anyway in an out-patient setting by GPs.

The median (IQR) lag time between EMA and AIFA approval and between AIFA and Sicilian Regional Drug Formulary Committee approval of studied drugs was 15.1 months (IQR: 10.9-21.5) and 3.6 months (IQR: 0.2-7.1) respectively. This delay could be due to AIFA and the MAH negotiation procedures, as pricing and reimbursement schemes in Europe must be negotiated by single Member States (Rossi et al, 2017). This delay may also be due to a decision by the MAH to submit a dossier for regional assessment only much later following approved by AIFA in view of market access strategies (Russo et al, 2010). Some notable delays, even up to 30 months, were seen between AIFA approval and Sicilian Regional Drug Formulary Committee approval. In addition to the above reasons, these delays may be due to commercial reasons, such as the MAH selling its license to other companies, and/or bureaucratic reasons, such as the committee giving lower priority to drug dossiers for drugs which will not be covered by the Sicilian healthcare system, compared to drugs that will be covered, or lengthy negotiations as to type of reimbursement class. Finally, such delays may also be due to legal appeals that are made by the drug company if the drug candidate is rejected for inclusion into the regional hospital formulary.

Irrespective of the cause, the delay in approval has important consequences in terms of limited and delayed access to new medicines in Italy compared to other European member states. This study shows that about 80% of the lag time between EMA and the Sicilian regional approval of medicines

is attributable to negotiation at the national level, that is, by the Italian drug agency. Nevertheless, Gori et al. suggest that the presence of different local formularies may lead to an important disparity in the access and use of pharmacological therapy in Italy. For example there are some Italian regions that do not have a regional formulary, so the time to patient access in these regions depends only on the time between EMA approval and AIFA marketing authorization (Gori et al, 2011). Drugs considered innovative by AIFA are partly covered by of the healthcare fund for innovation. Overall, among the 117 approved drugs, only 18 (15.4%) were judged innovative by AIFA and received fast track approval procedure. All of them belonged to ATC class L, J and M.

Monitoring registries are an important tool used by the Italian Drug Agency mostly to manage drug reimbursement based on MEA, especially for drugs used in specific therapeutic areas, such as oncology, rheumatology, neurology and gastroenterology (Montilla et al, 2014). On the other hand, at the moment drug-specific registries have been strongly underutilized for post-marketing assessment of benefit-risk profile in routine care which may potentially lead to altered conditions of use and price renegotiation.

During the study period, the drug classes having the greatest impact on the Sicilian regional budget were ATC group R (respiratory system drugs), ATC group L (antineoplastic and immunomodulating agents) and ATC group A (alimentary tract and metabolism drugs). Overall, 39.9% of the total estimated drug expenditure in the Sicily was due to drugs belonging to the ATC group R. In this particular case, this is likely due to the large number of patients eligible for drug therapy. Although oncology drugs were the second most expensive drug class, accounting for 38.9% of the total regional drug expenditure, the high cost is due to the cost of the drug rather than the number of eligible patients.

Strengths and limitations

This study has several strengths and limitations. This is the first study to systematically examine the lag time between EMA, AIFA and Regional Drug Formulary Committee approval as well as to explore in depth regional regulatory pathways leading to inclusion in the hospital drug formulary in Sicily and to estimate economic impact of newly marketed drugs during three observation years. An additional strength is the use of a broad range of information sources and documents concerning drugs for which the MAHs submitted a dossier to PTORS.

An important limitation of this study concerns the BIA, since there was a lack of information on the estimated number of eligible patients for 29 (25%) of the newly approved drugs, which led to an underestimation of total costs. Conversely, the cost might have been overestimated since we assumed one full year drug treatment, which might however be discontinued earlier in the real world setting. Furthermore, we did not consider MEAs in the calculation of the budget impact, which may also lead to an overestimation of the total costs. In addition, the BIA did not take into account any administration costs (e.g., ambulatory service tariffs, cost of syringes, cost of supervising medical staff) or adverse events (e.g., cost of hospitalization) and for drugs having multiple strength only the highest cost packages were considered. Therefore, economic analysis of newly marketed drugs should be considered only as exploratory. This study also does not take into account the lag time between drug approval time by the Sicilian Regional Drug Formulary Committee and its actual availability to patients in Sicily. Some of the marked lag times between AIFA approval and Sicilian Regional Drug Formulary Committee approval may be over-estimated. This may occur for the reasons highlighted earlier on, including the case that the drug dossier is not submitted to the committee immediately after AIFA approval. In theory this may happen for commercial reasons, such as a delay in negotiation of terms for drug availability, including pricing. Finally, the findings of the present study (in line with

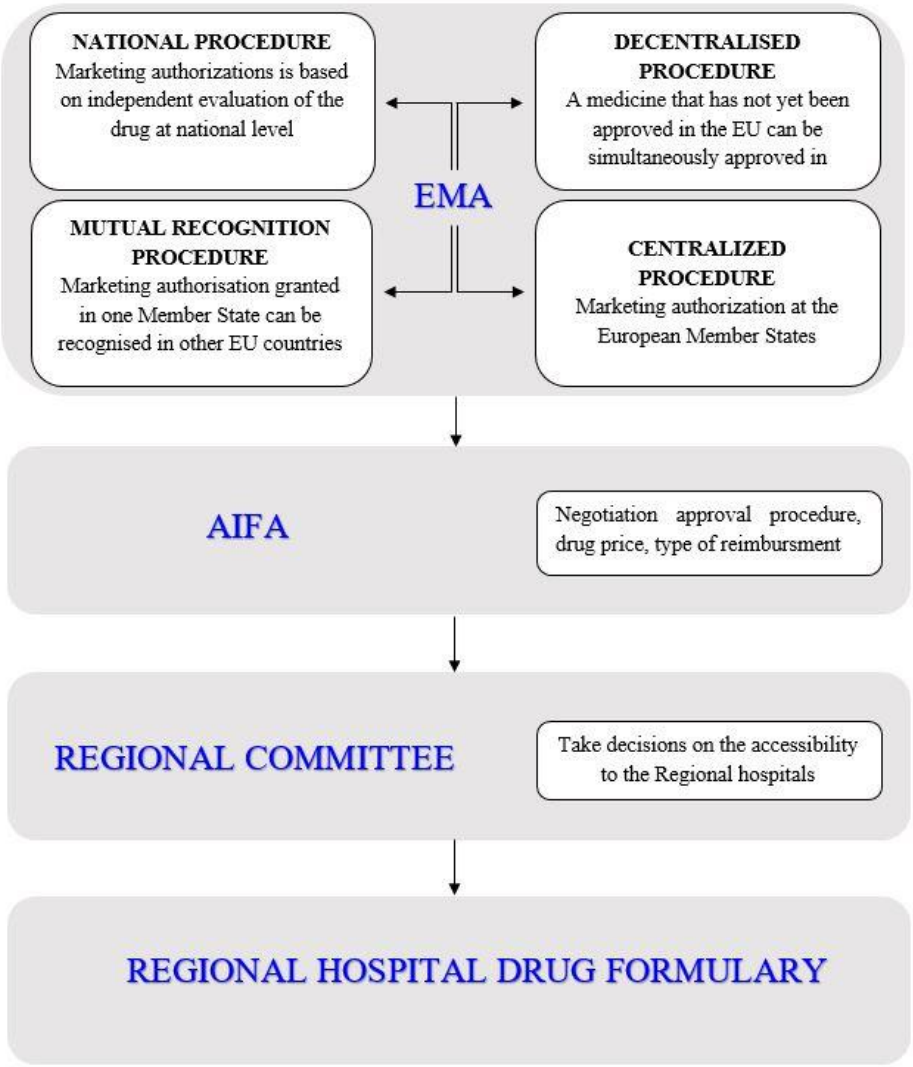
the OsMed Reports during the years 2012-2014) are specifically related to Sicilian Regional Drug Formulary Committee activities which may not reflect what occurred in other Italian Regions.

Conclusions

In the last three years the Sicilian Regional Drug Formulary Committee approved overall 170 drugs including extension of indication of use, even though only 15.4% (N=18) were granted innovative status. The drugs which were not included in the Regional Drug Formulary in most cases could be anyway reimbursed in the out-patient setting. Altogether these findings highlight that in no way were lifesaving and other essential drugs not made available to the patients at regional level.

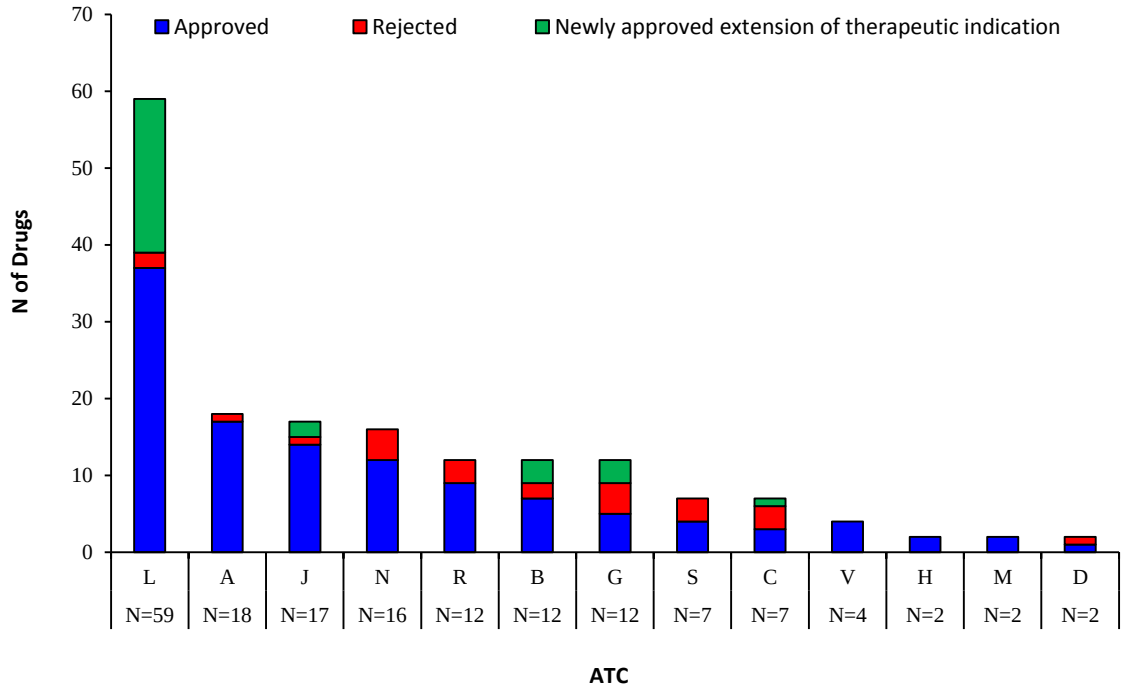
Most of the newly approved drugs during 2013-2016 years were highly costly medicines, especially biologic anticancer drugs, which were estimated to account for a pharmaceutical expenditure of over € 525 million only during the first year of treatment. Lag time between EMA and Sicilian Regional Drug Formulary Committee approval was mostly attributable to AIFA negotiation. Finally, for most of the high-cost newly approved medicines drug-specific registries were implemented upon AIFA request and in addition, the Sicilian Regional Drug Formulary Committee restricted the use of some drugs to qualified specialist centers which may be a good opportunity both to set up an effective post-marketing monitoring strategy with the ultimate goal of optimizing use as well as optimizing the expenditure of high-cost drugs at regional level.

Figure 1: Drug marketing pathway from EMA authorization to Regional formulary inclusion.



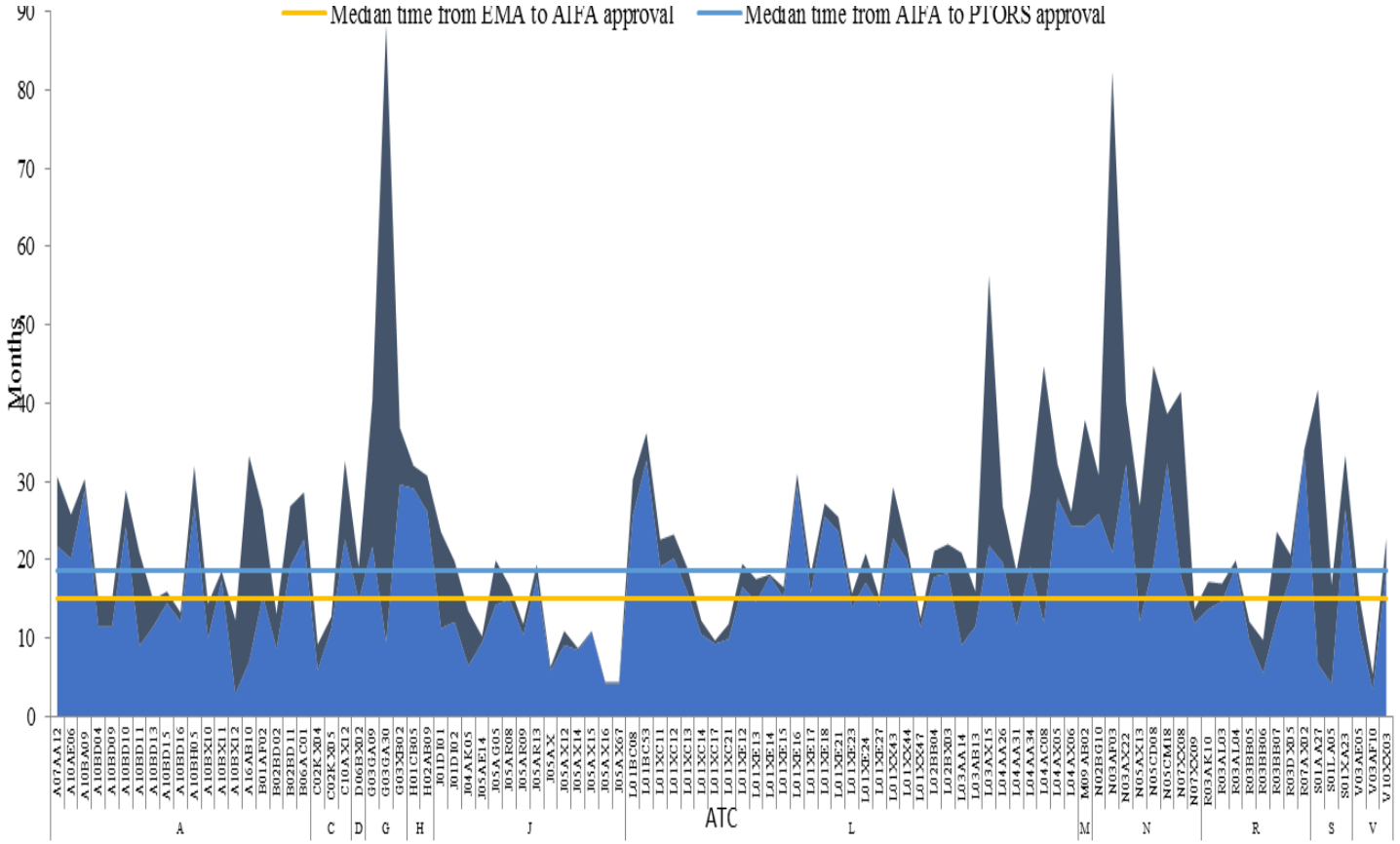
Legend. EMA=European Medicine Agency; AIFA= Italian Drug Agency.

Figure 2: Decisions of regional Drug Formulary Committee on requests for drug inclusions into the hospital formulary in the period 1st January 2013-1stApril 2016.



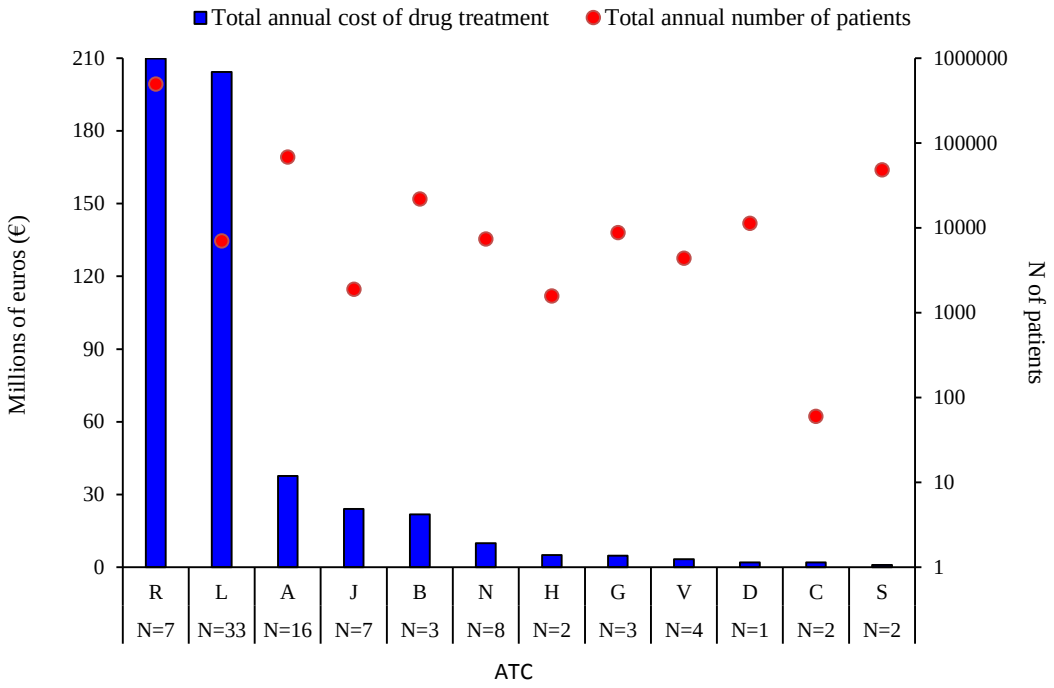
Legend. A=Alimentary tract and metabolism; B=Blood and blood forming organs; C=Cardiovascular system; D=Dermatological; G=Genito-urinary system and sex hormones; H=Systemic hormonal preparations, excluding sex hormones and insulins; J=Anti-infective for systemic use; L=Antineoplastic and immunomodulating agents; M=Musculo-skeletal system; N=Nervous system; R=Respiratory system; S=Sensory organs; V=Various. Newly approved drugs (N=117); Newly approved extension of therapeutic indication (N=29); Rejected drugs (N=24).

Figure 3: Lag time between the EMA marketing authorization date and Italian Drug Agency (AIFA) vs. Sicilian Regional Drug Formulary Committee approval dates.



Legend. A=Alimentary tract and metabolism; B=Blood and blood forming organs; C=Cardiovascular system; D=Dermatological; G=Genito-urinary system and sex hormones; H=Systemic hormonal preparations, excluding sex hormones and insulins; J=Anti-infective for systemic use; L=Antineoplastic and immunomodulating agents; M=Musculo-skeletal system; N=Nervous system; R=Respiratory system; S=Sensory organs; V=Various.

Figure 4: Budget impact analysis for total annual cost of newly approved drugs by Sicilian Regional Drug Formulary Committee during the first year of marketing in relation to the estimated number of treated patients, stratified by first ATC level.



Legend. ATC: Anatomical Therapeutic Chemical classification system; A=Alimentary tract and metabolism; B=Blood and blood forming organs; C=Cardiovascular system; D=Dermatological; G=Genito-urinary system and sex hormones; H=Systemic hormonal preparations, excluding sex hormones and insulins; J=Anti-infective for systemic use; L=Antineoplastic and immunomodulating agents; M=Musculo-skeletal system; N=Nervous system; R=Respiratory system; S=Sensory organs; V=Various.

*****Vpriv (ATC: A16AB10); Pradaxa (ATC: B01AE07); Xarelto (ATC: B01AF01); Novothirteen (ATC: B02BD11); Ferinject (ATC: B03AC01); Lojuxta (ATC: C10AX12); Cialis (ATC: G04BE08); Olysio (ATC: J05AE14); Triumeq (ATC: J05AR13); Harvoni (J05AX); Tivicay (ATC:J05AX12); Sovaldi (ATC: J05AX15); Exviera (ATC: J05AX16); Viekirax (ATC: J05AX67); Dacogen (ATC: L01BC08); Jevtana (ATC: L01CD04); Yervoy (ATC: L01XC11); Giotrif (ATC: L01XE13); Grazax (ATC: V01AA02); Nerixia (ATC: M05BA49); Xiapex (ATC: M09AB02); Vimpat (ATC: N03AX18); Campral (ATC: N07BB03); tecfidera (ATC: N07XX09); Incruse (ATC: R03BB07); Eylea (ATC: S01LA05) Nexplanon (ATC: G03AC08); and Dexdor (ATC: N05CM18) were excluded, because there is no information on the an estimate of the number of patients eligible for drug treatment. Nexplanon (ATC: G03AC08); Dexdor (ATC: N05CM18) and Aprokam (ATC: S01AA27) were excluded, because there is no information on the ex-factory cost.

Appendix A: Supplementary Methods Appendix

Pharmaceutical reimbursement classes in Italy

Drugs which are covered by national healthcare service (NHS) are classified into three different categories in Italy: Class A, which consists of drugs which are fully reimbursed by the NHS for out-patient use, Class H, which consists of drugs that are fully reimbursed but for in-hospital use only, and Class C, which includes drugs that are paid for out-of-pocket directly to the citizens. A specific category of the latter ones (C-OSP) is defined for drugs that can be used exclusively in a hospital setting or other healthcare facilities. Class A drugs can also be further classified into A-PHT (Hospital-Territory Formulary, Prontuario Ospedale-Territorio) and includes those medicines dispensed through direct distribution from hospital to outpatients to ensure hospital-community continuity of care.

Economic parameters used for calculating the budget impact

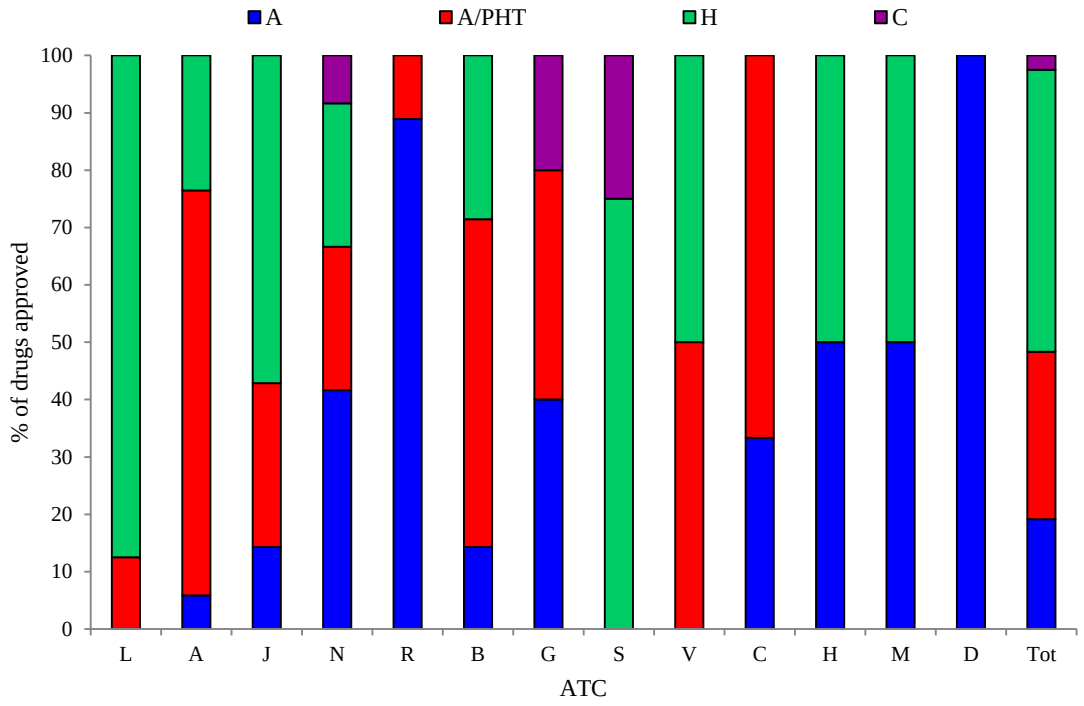
The total cost per patients was calculated by multiplying the drug cost (expressed in ex-factory price) for the number of packages of medicines per patient.

Drug costs information, expressed in ex-factory price, associated with each pharmaceutical specialty, was extracted on June 2016 from a national electronic drug compendium called *Compendio Farmaceutico Ospedaliero* that contains information on drugs marketed in Italy and dispensed only by hospital pharmacy. The number of drug pack-years per patient was estimated by dividing the dosage as defined in summary of product characteristics for the Dosage as defined in drug pack.

The proper dosage to achieve the desired effect was initially calculated according to the dosage and administration instructions in the summary of product characteristics as found in the national electronic drug compendium, assuming that dose was neither increased, nor decreased, without including information on pre-treatment or concomitant use of other drugs. For drugs where the duration of therapy was not clearly specified in the summary product characteristics a one-year treatment time was assumed. In the presence of injectable pharmaceutical formulations, we considered a standard body weight (70 kg) and a body surface area of the patient (1.8 m^2) was considered. For drugs with more than one therapeutic indication, the indication associated with a higher price was considered. Finally, the economic impact on the healthcare system was calculated by multiplying the cost per patients by the number of patients eligible for pharmacological treatment in Sicily using the information in the dossier presented to the regional drug formulary committee by the manufacturer).

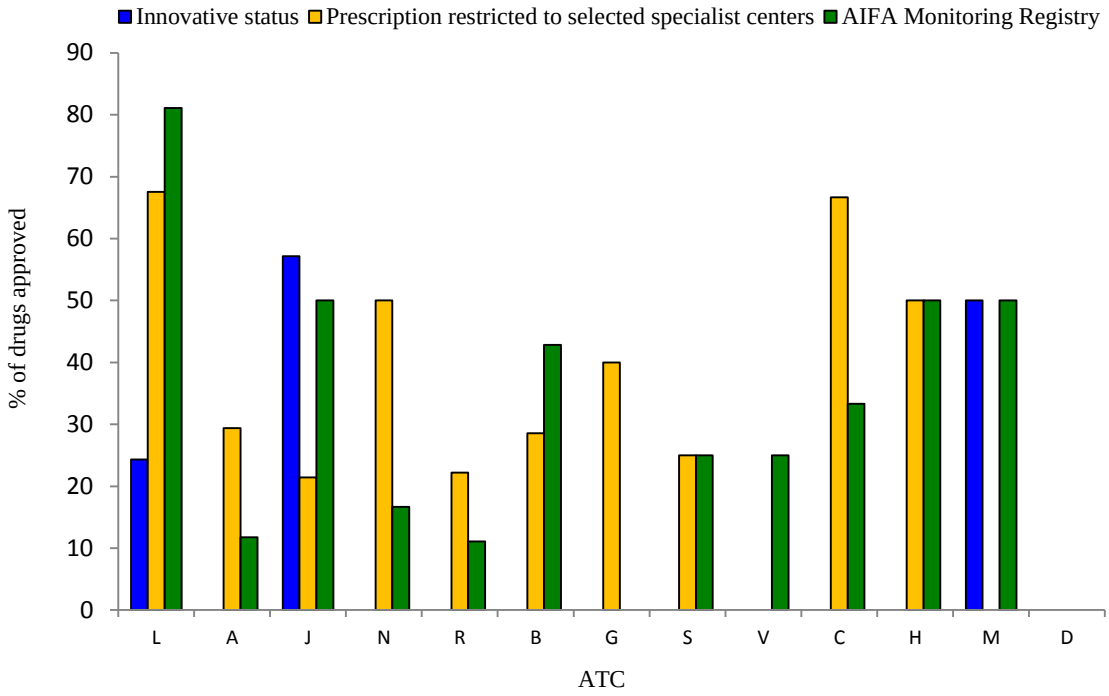
Appendix B: Supplementary figures and tables

Figure 1: Distribution of types of reimbursement classes for drugs approved by Regional Drug Formulary Committee, stratified by ATC I level.



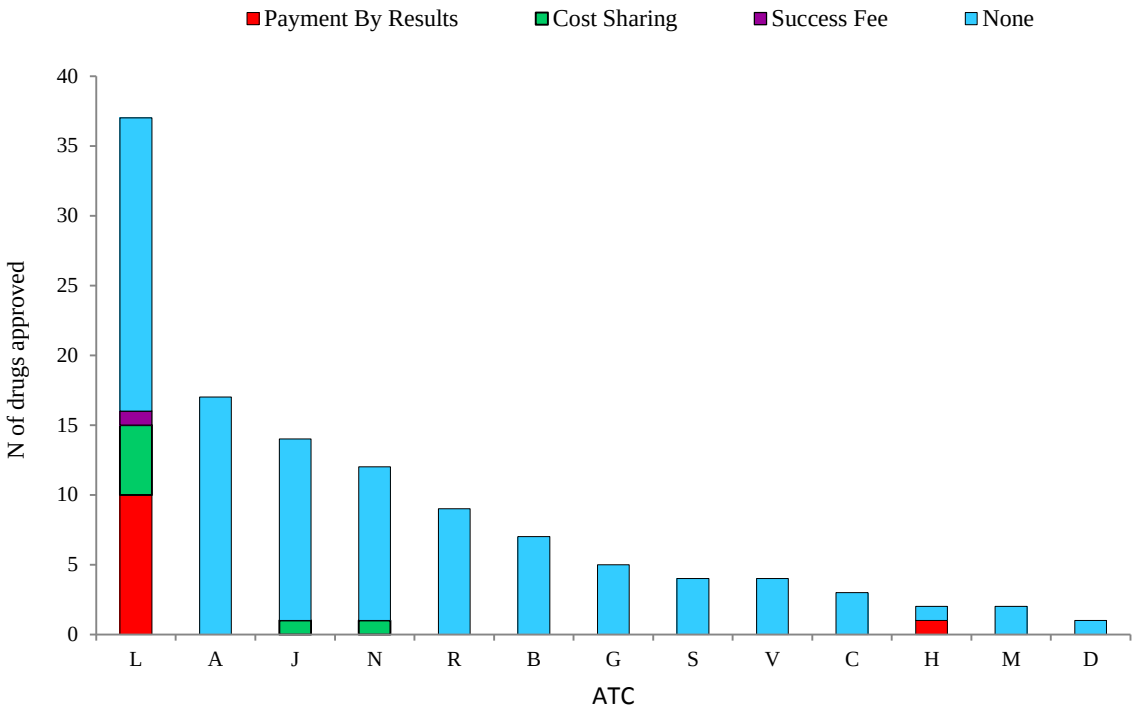
Legend. A=Alimentary tract and metabolism; B=Blood and blood forming organs; C=Cardiovascular system; D=Dermatological; G=Genito-urinary system and sex hormones; H=Systemic hormonal preparations, excluding sex hormones and insulins; J=Anti-infective for systemic use; L=Antineoplastic and immunomodulating agents; M=Musculo-skeletal system; N=Nervous system; R=Respiratory system; S=Sensory organs; V=Various; Class A= drugs which are fully reimbursed by the NHS for outpatient use; Class H= drugs that are fully reimbursed fort in-hospital use only; Class C= drugs that are charged directly to the citizens; A-PHT= drugs dispensed through direct distribution from hospital to outpatients to ensure hospital-community continuity of care.

Figure 2: Characteristic of drugs approved by the Sicilian Regional Drug Formulary Committee from 1st January 2013- 1st April 2016.



Legend. A=Alimentary tract and metabolism; B=Blood and blood forming organs; C=Cardiovascular system; D=Dermatological; G=Genito-urinary system and sex hormones; H=Systemic hormonal preparations, excluding sex hormones and insulins; J=Anti-infective for systemic use; L=Antineoplastic and immunomodulating agents; M=Musculo-skeletal system; N=Nervous system; R=Respiratory system; S=Sensory organs; V=Various.

Figure 3: Distribution of managed entry agreements for approved drugs by the Sicilian Regional Drug Formulary Committee during the period 1st January 2013- 1st April 2016, stratified by ATC first level.



Legend. A=Alimentary tract and metabolism; B=Blood and blood forming organs; C=Cardiovascular system; D=Dermatological; G=Genito-urinary system and sex hormones; H=Systemic hormonal preparations, excluding sex hormones and insulins; J=Anti-infective for systemic use; L=Antineoplastic and immunomodulating agents; M=Musculo-skeletal system; N=Nervous system; R=Respiratory system; S=Sensory organs; V=Various; Payment By Results= full reimbursement from the manufacturer in case of therapeutic failure; Cost Sharing= price discount on the first therapy cycles for all patients eligible for the treatment; Success Fee=full reimbursement only for therapeutic success.

Table 1: Form for the drug dossier assessment by the members of the Sicilian Regional Drug Formulary Committee.

Active principle	ATC	Reimbursement categories	Prescriber	Indication of drug use	Posology	Newly approved extension of therapeutic indication	Alternative therapeutic drugs	Innovativeness	AIFA Monitoring Registry	Number of patients treated	Prevalence of disease in Sicily	Budget impact (first year)

Assessment of the drug dossier by the Sicilian Regional Drug Committee is based on evaluation of drug-specific forms summarizing key information on clinical and economic aspects of the drug as compared to the available alternative options. Based on this information each individual member of the Committee filled an evaluation score concerning several parameters before monthly meetings.

Table 2: Form summarizing the independent scientific literature concerning mostly indication of use-specific pre-marketing phase 3 randomized controlled trials (RCTs) and international HTA agencies used by Sicilian Regional Drug Formulary Committee.

Study title	Sponsor	Study design	Authors, Year, Journal	Population studied	Exposure	Outcome	Results

Legend: Phase 3 RCTS are used to provide an evidence base informing the decision on which drugs to approve, with evidence being identified in Medline and Cochrane databases. If Phase 3 trials are not available, Phase 2 trials or the closest equivalent is used. Further information on safety and efficacy is obtained from Scottish Medicine Consortium, Australian Prescriber, *Prescrire* in English, Nice and University of York and similar sources. Emphasis is placed on the indication for which the drug is requesting approval. Abbreviation: HTA- health technology assessment.

Table 3: Form summarizing the independent scientific literature concerning mostly indication of use-specific pre-marketing phase 3 RCTs and international HTA agencies used by Sicilian Regional Drug Formulary Committee.

Agency/No-Profit Organization and Publication Date	Decision

Abbreviation: HTA- health technology assessment.

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Chapter 3: Biologic drugs in the research pipeline: pediatric clinical trials

To be submitted as a short report

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Abstract

Introduction: Although it is essential to understand the state of the art regarding drug approvals and clinical trials investigating the efficacy of oncologic drugs in children, there is currently no published study describing this. The aim of this study was to describe which drugs have been approved in the pediatric population with oncologic indication from 2006 to 2017, and to describe the clinical trials which are being conducted concerning these drugs.

Methods: The Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites were searched for active principles having an oncological indication for pediatric patients that were approved from January 2006 to September 2017. Furthermore, two websites were searched for information on clinical trials in pediatric populations, namely clinicaltrials.gov and the European Union Clinical Trials Register. The search in these two databases was carried out from the inception date of the databases to September 2017. The approved drugs and the clinical trials identified were described.

Results: From January 2006 to September 2017, EMA and FDA granted a marketing authorization to 8 drugs with pediatric oncology indications each, for a total of 16. The most recent years saw a larger number of these drugs being approved. A total of 247 clinical trials in pediatric populations for drugs having oncological indications was identified. The European website contained 100 (40.5%) of these protocols while the American website contained 147 (59.5%) protocols. Overall, 46 trials concerned biologic drugs (18.6%), 145 concerned non-biologic drugs (58.7%) and 56 studied biologic and non-biologic drugs (22.7%). The most commonly studied single disease was acute myeloid leukaemia (25.5% of all identified trials). Approximately only 11% of all trials were phase III trials.

Conclusion: EMA and FDA have approved a similar number of drugs for oncologic use in children in the last 10 years. While this may suggest significant pre-marketing clinical research, a comparatively small number of trials were phase III trials. Given that drugs for pediatric use may be approved before phase III trials are conducted, it is imperative to analyze the quality and the results of such trials very carefully.

Introduction

Although there is an increasing number of medicines approved for pediatric patients, there are comparatively fewer drugs approved for an oncology-related indication in children. Although in recent years there seems to be a growing number of drugs for children having an oncology-related indication (Tomasi et al., 2017). In fact, Tomasi et al. show that the number of new medicines with a pediatric indication and the number of new pediatric indications, more than doubled, from 2007 to December 2016 in Europe. However, this number of likely to be much smaller concerning oncology-related indications. There is currently no published evidence on the number and type of oncological drugs recently approved in children.

In view of the special needs associated with pediatric populations, including a potential greater susceptibility to a larger array of adverse drug reactions and variations in drug effectiveness, the European Medicines Agency (EMA) has proposed that drug companies should submit a pediatric investigation plan (PIP) to monitor the pediatric population prior to drug marketing authorization approval. Although it is essential to understand the state of the art regarding clinical trials investigating the efficacy of oncologic drugs in

children, there is currently also no published study describing this.

In view of the above, the aim of this study was to describe which drugs have been approved in the pediatric population with oncologic indication from 2006 to 2017, and to describe the clinical trials which are being conducted concerning these drugs.

Methods

Identification of pediatric drug approval

The Food and Drug Administration (FDA) "Approved Drug Products" webpage and EMA websites were searched for active principles having an oncological indication for pediatric patients that were approved from January 2006 to September 2017 (last data extraction date). For the approved drugs selected, information on the year of approval, whether it was a biologic drug or not, specific pediatric indication and where possible, and whether the drug was also approved in adults was noted.

Identification of clinical trials in pediatric populations for oncological indications

Two websites were searched for information on trials in pediatric populations, namely clinicaltrials.gov, which contains a database of privately and publically funded clinical trials made available by the United States National Library of Medicine, and the European Union Clinical Trials Register, which contains a database made available by the European Medicines Agency. These two databases contain information on clinical trials from around the world, and not only from the countries in which they are based. The search in the two database was carried out from the inception date of the databases to September 2017. No temporal exclusion criteria were used. Trials were included if the disease under study was oncological and if the population included children. Trials not recruiting children exclusively (i.e., trials recruiting children and adults) were included but trials recruiting adult populations (aged 18 and over) were excluded. Trials were also included if the intervention consisted of cytotoxic drugs (e.g., alkylating drugs, anthracyclines, antimetabolites, vinca alkaloids etc.), biologic drugs and/or gene therapy. Trials containing a combination of these

drugs, as opposed to one of these drugs (monotherapy) were included. However trials where the intervention consisted of hematopoeitc or allogenic stem cell transplantation were not included.

For trials meeting the inclusion criteria, the online protocols were searched for the following information: trial phase, whether the trial was still ongoing, the disease under study and whether there was more than one disease under study, study drug. Trial protocols indicating more than one trial phases were counted more than once, in the respective trial phases and in a field denoted "more than one phase". Study drugs were classified by type as biologic or non biologic for study drugs (for monotherapy, where the study drug was a biologic/non-biologic; for polytherapy, where all drugs were biologic/non-biologics) and biologic and not biologic in combination. In each of these classifications, we considered only the intervention drugs, and not the comparator. The population in the trial was classified as pediatric or pediatric and adult populations together. Diseases under study were classified as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), other single disease and more than one disease under study.

The number and frequency of trials in the various categories above was estimated, first stratifying by type of study drug and then stratifying by disease under study.

Results

Identification of pediatric drug approval

From January 2006 to September 2017, EMA and FDA granted a marketing authorization to 8 drugs with pediatric oncology indications each, for a total of 16 (**Table 1**). The most recent years saw a larger number of these drugs being approved. In 2017, FDA approved 3 (37.5%) drugs for pediatric patients, 2 of which were biological drugs (25.0%): blinatumumab for ALL and pembrolizumab for Hodgkin lymphoma. EMA only approved 1 drug for oncologic indication in children (12.5%) in 2017. Among the 8 drugs approved by the FDA, 50% were biologics, while of the 8 approved by EMA, 37.5% were biologics. The oncological indication for which most drugs were approved for children by the FDA was acute lymphoblastic leukemia (ALL), at 62%. EMA also has approved a relatively large number of drugs for ALL, at 50% of approved pediatric drugs for oncological indications over the study period.

Identification of clinical trials in pediatric populations for oncological indications

Overview of drugs investigated

A total of 247 clinical trials in pediatric populations for drugs having oncological indications was identified. The EMA website contained 100 of these protocols while the U.S. National Library of Medicine contained 147 protocols. Overall, 46 trials studied biologic drugs (18.6%), 145 studied non-biologic drugs (58.7%) and 56 studied biologic and non-biologic drugs (22.7%) (**Table 1**). Among trials with only one study drug, 37 (15.0%) were already approved for use in the pediatric population for any indication, while 46 were not (18.6%) don't have approval (data not shown). Among the trials with multiple study drugs, 51 drugs (20.6%) were all approved for use in pediatric patients for any indication, while 113 had at least one unapproved drug (45.7%)(data not shown.

Among studies investigating non-biologics, the majority were phase I trials (N=55; 37.9 %) (**Table 2**). A total of 38 trials (26.2%) were carried out only in a pediatric population, while 107 trials (73.8%) were performed on both pediatric and adult patients. Still among non-biological drugs, 71 trials (49.0%) concern more than one disease, while only one disease was studied in 74 trials (51.0%).

On the other hand, among the trials investigating biologic drugs, most trials were phase II trials 45.7% (N=21). Among the 46 trials investigating biological drugs, 13 (28.3%) trials were performed only on the pediatric population, while the majority, 33 of trials (71.7%) were performed on pediatric and adult patients. Half of the trials investigating biologic drugs concerned more than one indication (N=23, 50%).

A total of 56 trials (22.7%) concerned a combination of biologic and non-biologic study drugs. A total of 14 trials (25.0%) were carried out only in a pediatric population, while 42 trials (75.0%) were performed on both pediatric and adult patients. Still among biologic and non-biological drugs, 26 trials (46.4%) concern more than one disease, while only one disease was studied in 30 trials (53.6%).

Overview of diseases investigated

As for the individual diseases, most of the trials investigated ALL (N=63, 25.5%). Even for ALL, most of the trials were in phase I (N=21, 33.3%) and were mostly carried out in both the pediatric and the adult population (N=38, 60.3%). Regarding ALL, there were 12 trials where the intervention drug consisted of biological drugs (19.1%).

A large proportion of trials were carried out to investigate more than one disease (N=121, 49%), and mostly belong to phase I (N=53, 43.8%) and phase II (N=53, 43.8%). Of these trials, 23 (19.0%) studied biological drugs. Even in this case, the pediatric and adult population together was the most studied (N=99, 81.8%).

Biological drugs were studied in 8.3% of AML trials, in 19.1% of the HL trials, in 25% NHL trials and in 19.2% of other single disease trial. Diseases included in this latter category were: myeloid leukemia, acute leukemia, T and pre B Cell lymphocytic leukemia, anaplastic large cell lymphoma, hereditary medullary thyroid cancer, acute lymphocytic leukemia.

Most trials were ongoing, ranging from 42% for “other single diseases” to 91% for AML.

Discussion

Main findings

One of the main findings of this study is that the number of biologic drugs approved by both FDA approved and EMA is growing, but the FDA approved of these drugs than EMA, especially in 2017. The FDA has extended medication indications for drugs such as pembrolizumab and blinatumumab for use in the pediatric population. In addition, in August 2017 the FDA approved tisagenlecleucel, a particularly innovative therapy. Unlike most cancer therapies that are identical from patient to patient, CAR-T therapies are made by removing the T cells of a patient, genetically modifying them to respond to certain targets expressed on the patient’s cancer cells, and then reinfusing the cells (Bach B.B. et al, 2017). When the T cells come into contact with the target (CD19 in the case of ALL), they proliferate while secreting a number of programmed substances including inflammatory cytokines that destroy the cancerous cells. Response rates are impressively around 80%, with 25% of patients recurring within 6 months, and 1-year survival of 80%. Alternative treatments do not achieve these types of results (Bach B.B. et al, 2017). The price of a

single treatment of tisagenlecleucel is $475 000, much higher than any other cancer treatment, so it should be monitored.

The results of our search for clinical trials confirm that the most commonly studied oncologic disease among children is ALL. This is also the disease for which several drugs were approved by EMA and the FDA during our study period. The studies found are mostly phase I or II trials, but it is unlikely for pediatric trials to pass to phase III. Half of FDA-approved drugs were biological, suggesting that clinical research was very active for these drugs but there were very few phase III biological drugs. It is worth noting that most of the studies conducted are also carried out on adults and that, even though the drugs may be destined for use in children, these are often not the exclusive trial populations. A large proportion of the trials identified did not have information on the phase of the trial. This may indicate a poor quality of the protocol, at least as far as the public version is concerned. Accuracy in reporting is essential to improved the transparency of research. Furthermore, for a large number of trials, results were not available.

Strengths and limitations

The present study has several strengths as well as limitations. To our knowledge this study is the first to offer an updated overview of the drugs that have been approved by EMA and the FDA for oncological indications in children. It is also the first to our knowledge to examine the trials that have been conducted for cancer treatment in children. These two approaches have allowed us to have a good overview of the state of the art concerning innovative drug approval as well as the clinical research before drug approval, on a global scale. This study also has some limitations. We restricted the study to hematologic diseases as the main study disease, because these are most common in children unlike solid tumors. Information on solid tumors was only collected if a trial where the main disease was hematologic also studied solid tumors. Some of these trials were conducted on both the pediatric and the adult population, so phase III trials are likely to have been conducted on adults. These trials would not have been captured since the search was restricted to pediatric populations.

Conclusions

The FDA and EMA have approved a similar number of oncologic drugs for children. However, EMA has approved fewer drugs in 2017 compared to EMA. While this may suggest significant pre-marketing clinical research, a comparatively small number of trials were phase III trials. Given that drugs for pediatric use may be approved before phase III trials are conducted, it is imperative to analyze the quality and the results of such trials very carefully. Approximately half of the new drugs approved for oncologic indications in children were biologics. Of the trials investigating haematologic cancer treatment in children, 46 trials studied biologic drugs (18.6%), 145 studied non-biologic drugs (58.7%) and 56 studied biologic and non-biologic drugs (22.7%). Most of the trials concerning biologic drugs were phase II trials.

Table 1. Newly approved drugs for oncologic indications among pediatric patients, between 2006-2017.

	Medicinal product	Active substance	Biologic	Year of authorisation	Pediatric indication	Population
FDA	Oncaspar	Pegaspargase	No	2006	ALL	Pediatric
	Eusa	Erwinaze (asparaginase erwina chrisantemi)	No	2011	ALL	Pediatric and adult
	Xgeva	Denosumab	Yes	2013	Giant cell bone tumor	Adolescent and adult
	Purixan	6-mercaptopurina	No	2014	ALL	Pediatric and adult
	Unituxin	Dinutuximab	Yes	2015	Neuroblastoma	Pediatric
	Blincyto	Blinatumomab	Yes	2017	ALL	Pediatric and adult
	Keytruda	Pembrolizumab	Yes	2017	HL	Pediatric and adult
	Kymriah	Tisagenlecleucel	No	2017	B cell ALL	Pediatric and young adult
EMA	Evoltra	Clofarabine	No	2006	ALL	Pediatric
	Mepact	Mifamurtide	No	2009	Osteosarcoma	Pediatric and adult
	Xgeva	Denosumab	Yes	2011	Giant cell bone tumor	Adult and adolescent
	Caprelsa	Vandetanib	Yes	2012	Medullary thyroid cancer	Pediatric and adult
	Xaluprine	6-mercaptopurina	No	2012	ALL	Pediatric, adolescent and adult
	Spectrila	Asparaginasi	No	2016	ALL	Pediatric and adult
	Oncaspar	Pegaspargase	No	2016	ALL	Pediatric and adult
	Apeiron	Dinutuximab beta	Yes	2017	Neuroblastoma	Pediatric and adult

Abbreviations:

FDA= Food and drug administration

EMA= European medicines Agency

ALL= acute lymphoblastic leukemia

B cell ALL= b cell acute lymphoblastic leukemia

HL = Hodgkin lymphoma

Table 2. Trials conducted in pediatric populations using any study drugs, as identified in clinicltrials.gov and EU clinical trial register.

	Trials conducted in pediatric populations using any study drugs N=247		
	Biologic study drug N= 46 (18.6%)	**Non biologic study drug N= 145 (58.7%)**	**Biologic and non biologic study drug N=56 (22.7%)**
Trial phase			
I	15 (32.6%)	55 (37.9%)	22 (39.3%)
II	21 (45.7%)	46 (31.7%)	36 (64.3%)
III	5 (10.9%)	16 (11.0%)	7 (12.5%)
More than one phase[1]	7 (15.2%)	17 (11.7%)	14 (25.0%)
Not specified	12 (26.1%)	45 (31.0%)	5 (8.9%)
Disease under study			
1 disease	23 (50%)	74 (51.0%)	30 (53.6%)
>1 disease	23 (50%)	71 (49.0%)	26 (46.4%)
Population			
Paediatric only (until 17 years)	13 (28.3%)	38 (26.2%)	14 (25.0%)
Pediatric and adult	33 (71.7%)	107 (73.8%)	42 (75.0%)

Table 3. Trials conducted in pediatric populations for any oncologic indication

	Trials conducted in pediatric populations for any oncologic indication N=247					
	ALL N= 63 (25.5%)	**AML N= 12 (4.9%)**	**HL N= 21 (8.5%)**	**NHL N= 4 (1.6%)**	**Other single disease* N= 26 (10.5%)**	**More than 1 disease** N= 121 (49.0%)**
Trial phase						
I	21 (33.3%)	4 (33.3%)	4 (19.1%)	1 (25%)	9 (34.6%)	53 (43.8%)
II	20 (31.8%)	2 (16.7%)	14 (66.7%)	1 (25%)	13 (50.0%)	53 (43.8%)
III	7 (11.1%)	2 (16.7%)	5 (23.8%)	1 (25%)	1 (3.8%)	12 (9.9%)
More than one phase	10 (15.9%)	1 (8.3%)	4 (19.0)	-	4 (15.4%)	19 (15.7%)
Not specified	25 (39.7%)	5 (41.7%)	2 (9.5%)	1 (25%)	7 (26.9%)	22 (18.1%)
Type of study drug						
Biologic	12 (19.1%)	1 (8.3%)	4 (19.1%)	1 (25%)	5 (19.2%)	23 (19.0%)
Non biologic	38 (60.3%)	9 (75.0%)	8 (38.1%)	3 (75%)	15 (57.7%)	72 (59.5%)
Biologic and non biologic	13 (20.6%)	2 (16.7%)	9 (42.9%)	-	6 (23.1%)	26 (21.5%)
Population						
Paediatric only (until 17years)	25 (39.7%)	9 (75.0%)	3 (14.3%)	1 (25%)	5 (19.2%)	22 (18.1%)
Pediatric and adult	38 (60.3%)	3 (25.0%)	18 (85.7%)	3 (75%)	21 (80.8%)	99 (81.8%)
Trial status						
Ongoing	40 (63.5%)	11 (91.7%)	15 (71.4%)	2 (50%)	11 (42.3%)	62 (51.2%)
Completed or suspended	23 (36.5%)	1 (8.3%)	6 (28.6%)	2 (50%)	15 (57.7%)	59 (48.8%)
Trial outcome						
Results available	12 (19.1%)	-	4 (19.1%)	1 (25%)	9 (34.6%)	20 (16.5%)

Abbreviations:

ALL= acute lymphoblastic leukemia

AML= acute mieloyd leukemia

HL = Hodgkin lymphoma

NHL= Non Hodgkin lymphoma

* myeloid leukemia, acute leukemia, T and pre B Cell lymphocytic leukemia, anaplastic large cell lymphoma, hereditary medullary thyroid cancer.

** Chronic lymphoblastic lymphoma, Follicolar lymphoma, waldenstrom macroglobulinemia, wilms tumor, kidney cancer, hepatoblastoma, osteosarcoma, acute lymhpblastic leukemia, chronic myelid leukemia, acute myeloid leukemia, multiple myeloma, T cell ALL, B cell ALL, neuroblastoma, medulloblastoma, glioma, hbadomyosarcoma, myelodisplastic syndrome, Hodgkin lymphoma, non Hodgkin Lymphoma, juvenile myelomonocytic leukemia, Burkitt lymphoma, erwing sarcoma, anaplastic large cell lymphoma

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Chapter 4: Prevalence of use and cost of biological drugs for cancer treatment: a 5 years' picture from Southern Italy

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Abstract

Background and Objectives: Considering the clinical and economic burden of biological drugs in cancer treatment, it is necessary to explore how these drugs are used in Italian routine care and how they affect the sustainability of the NHSs. This study aimed at investigating the prevalence of use and costs of biological drugs for cancer treatment in a general population of Southern Italy in the years 2010-2014.

Methods: This was a retrospective, observational study, using healthcare administrative databases of Messina Province, during the years 2010-2014. Users of biological drug for cancer treatment were characterized; the prevalence of use and costs were calculated over time. The potential impact of biosimilars on the expenditure was estimated.

Results: Considering 653,810 residents in Messina area in the study years, 2,491 (0.4%) patients received at least one study drug. The most frequently used were monoclonal antibodies (mAbs) (N=1,607; 64.5%), and tyrosine kinase inhibitors (TKIs) (N=609, 24.4%). mAbs were mainly used by females (60.3%), for metastasis due to unspecified primary tumor, lymphomas or breast cancer (24.2%, 16.7% and 13.7%, respectively). Most of small molecules users were males (56.3%), treated for multiple myeloma, metastasis due to unspecified primary tumor, leukemia and lung cancer (13.1%, 12.6%, 9.5% and 8.9%, respectively).
During the study years, the prevalence of use doubled from 0.9 to 1.8 per 1,000 inhabitants; likewise, the expenditure grew from 6.6 to 13.6 million Euros. Based on our previsions, in 2020 this expenditure will grow up to € 25.000.000. Assuming a 50% biosimilar uptake (trastuzumab and rituximab), a potential yearly saving of almost 1 million Euros may be reached.

Conclusions: In recent years, the use and costs of biological drugs in cancer patients dramatically increased in a large population from Southern Italy. This trend may be counterbalanced by adopting biosimilars, once available. Claims databases represent a valid tool to monitor the uptake of newly marketed biological drugs and biosimilars.

Key points:

- In the last years, the use of biological drugs for cancer treatment rapidly increased and the corresponding costs almost doubled from 6.6 to 13.6 million Euros
- Based on our previsions, in 2020 this expenditure will grow up to 25 million Euros and the use of biosimilar may provide an annual saving of around 1 million Euros
- Claims databases may represent a valid tool to monitor the uptake of newly marketed biological drugs and biosimilars

Introduction

Biological drug contains one or more active substances that may be produced or extracted from a biological system or through biotechnological procedures (European Medicine Agency, 2012; Italian Medicine Agency, 2013).

In the last years, biological drugs changed dramatically the pharmacological management of several high burden diseases including specific cancer types. Most of the recently marketed drugs in oncology are monoclonal antibodies and tyrosine-kinase inhibitors, which are highly innovative as targeting specific molecules necessary for tumor growth and progression (Mach, 2012).

Considering the clinical and economic burden of biological drugs also in cancer treatment, it is necessary to explore how these drugs are used in routine care and how they affect the sustainability of the National Health Services (NHSs). Once a biological drug loses its patent, the corresponding biosimilar may enter the market, thus guaranteeing an average 20-30% lower purchase cost than originators (Buske et al, 2017). To date, the only biosimilar that has been already approved by the European Medicine Agency (EMA) for cancer treatment is rituximab (2017), while biosimilar trastuzumab and bevacizumab are still currently under review (Gabi Journal, 2017).

The marketing of biosimilars may represent a great opportunity for saving money (Renwick et al, 2016), and post-marketing monitoring systems using real world data may be helpful for the assessment of their impact in clinical practice.

The aim of this observational study was to analyze the use and costs of biologic drugs for cancer treatment of a large area of Southern Italy in the years 2010-2014. In addition, possible economic saving due to marketing of biosimilars for cancer treatment in future years was estimated.

Methods

Data source

This observational, retrospective, observational study was conducted using data extracted from the healthcare administrative databases of Messina Local Health Unit, "G. Martino" Hospital and *Papardo* Hospital, during the years 2010-2014 (from 2011 to 2014 for *Papardo* Hospital). All these centers provided information on total use of biological drugs for cancer treatment from all residents in Messina Province (Southern Italy).

In each center, specific databases collect anonymous data related to all the drugs reimbursed by the NHS and dispensed to both inpatients and outpatients. Data about drug dispensed to inpatients are recorded by the specific ward as aggregate data (not at individual level), and were therefore not used for this study. Considering outpatients, the systemic biological drugs administered as subcutaneous injections or orally, are dispensed by the hospital pharmacists to the patient, who will self-administer the drug. Systemic biological drugs administered as intravenous infusion are exclusively administered in the hospital setting, even to outpatients. However, the dispensing of biological drugs to outpatients is recorded at patient-level through the dispensing database, which is routinely implemented by the hospital pharmacy. This database includes data about the dispensed drug (i.e., market authorization code, brand name, Anatomical Therapeutic Chemical [ATC] classification system code, number of dispensed packages), the patient (date of birth, sex, citizenship, potential co-payment exemption codes), date of dispensing and costs.

Each of the three center has its own dispensing data flow, which is implemented independently from the other centers. Furthermore, dispensing databases are generated for administrative reasons, and they routinely undergo quality checks, in order to avoid duplicates. Users of the study drugs were

identified and assigned an anonymous and unique identifier, thanks to which other claims databases including hospital discharge diagnoses were linked.
Claims databases containing hospital discharge diagnosis are coded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD9-CM).

Study population
All residents in the catchment area of Messina Province during the years 2010–2014 were considered. From this source population, all patients receiving at least one dispensing of any of the study drugs during the study period were identified.

Study drugs
The biological drugs approved for cancer treatment and available in Italy during the study years were classified into monoclonal antibodies (mAbs), fusion proteins, immunomodulatory agents and small molecules, the latter ones further categorized as tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin inhibitors (mTOR-i) and proteasome inhibitors. A complete list of the study drugs and related indications for use is available in Table S1.

Data Analysis
Data about the study drugs users were entirely anonymized and pooled. The index date (ID) was identified as the first date of a study drug dispensing during the study years.
As the overall population is dynamic during a calendar year, the prevalence of the study drugs use was calculated as the number of study drug users (i.e. patients receiving at least one study drug during the years 2010-2014) divided by the the estimates of the total number of residents in the catchment area provided by the National Statistics Office for each study year, stratified by calendar year and type of drug. For each calculated prevalence of use, lower and upper bounds of the corresponding 95% confidence interval were computed following the Wilson score interval (Wilson, 1927). In addition, pharmaceutical expenditure of the study drugs were measured over time and stratified by type of biological drug.
Users of different types of biological drug were characterized, in term of age and sex, type of cancer and previous use of chemotherapeutics. The type of cancer was identified based on the last ICD9-CM diagnosis code of tumor, registered in the hospital discharge diagnosis database within six months prior to the ID. The distinction between primary (i.e. the original site of the tumor) and secondary tumor (i.e., any additional sites where the tumor has spread, also called metastases of primary tumors) was possible using the specific ICD9-CM codes. The median number of dispensing per patient was calculated.
Moreover, costs related to the study drugs dispensing were calculated over time and a prediction of the expected expenditure sustained by public hospitals in Messina area until 2020 was performed. Data about the pharmaceutical expenditure for the study drugs in the years 2015-2016 were provided by the considered centers. Given the available costs-related information for the years 2010-2016, a linear trend (that expresses data as a linear function of time) in the expenditure sustained by the three centers of Messina area was estimated (equation: $y= 2E+06x + 5E+06$; $R^2= 0.9966$). In particular, it allowed us to determine if measurements exhibit an increasing trend which is statistically distinguished from random behaviour. Through statistical extrapolation of data for the years 2017-2020 (in the respect of assumption of linear trend, independence of observations and homoscedasticity), the baseline trend (i.e., the red dashed line in the figure) was calculated (scenario

n. 1). Considering the impact of rituximab and trastuzumab on the yearly expenditure (35%), we calculated the pharmaceutical expenditure until 2020, assuming both biosimilar rituximab and trastuzumab were 25% cheaper than the corresponding reference products and hypothesizing an uptake equal to 20%, 50% and 80% of the total amount of consumption of the two biological drugs (respectively, scenarios n. 2-3-4).

Ethics Statement

This study was conducted in the context of the "Progetto Osservazionale sulla Psoriasi – SOPso" project. The study protocol was notified to the Ethical Committee of the Academic Hospital of Messina, in agreement with the current national legislation (Italian Medicine Agency, 2007). This study received unconditional funding from Novartis which did not interfere in any stage of the study.

All statistical analyses were conducted using SAS for Windows, Version 9.3. Figures were created using Microsoft Office.

Results

Overall, on a total population of 653,810 residents in the catchment area of Messina area during the years 2010-2014, 2,491 (0.4%) patients had at least 6 months of database history and received at least one study drug for cancer treatment.

The most frequently used were mAbs (N= 1,607; 64.5%), followed by TKIs (N= 609, 24.4%) (Table 1). mAbs were mostly dispensed for the treatment of metastasis due to unspecified primary tumor (24.2%), lymphomas (16.7%), breast cancer (13.7%) and colorectal cancer (9.2%); most of mAb users were females (60.3%) and were 45-64 years old (47.2%). Small molecules users were more likely to be males (56.3%) and to be slightly older (65-79 years old: 45.7%), receiving the study drugs mostly due to multiple myeloma, metastasis due to unspecified primary tumor, leukemia and lung cancer (13.1%, 12.6%, 9.5% and 8.9%, respectively). No users of fusion proteins or immunomodulatory agents could be identified during the study years, and these two categories were therefore not included in Table 1.

During the study years, the total prevalence of use of biological drugs for cancer treatment doubled from 0.9 (in 2010) to 1.8 per 1,000 inhabitants (in 2014), mostly due to the increased use of small molecules (+120.8%) rather than mAbs (+88.4%) (Figure 1, Table S2).

Accordingly, the costs of the biological drugs for cancer treatment rapidly grew during the study years in Messina province from 6.6 million Euros in 2010 (N. users = 591) to 13.6 Euros in 2014 (N. users = 1,150), for a total expenditure of around 50 million Euros during the five observation years (Figure 2). Likewise, the number of different biological drugs that were prescribed to the study population increased from 17 in 2010 to 21 in 2014 (data not shown).

In 2020, based on our previsions, the expenditure for biological study drugs will grow up to € 25 million. Assuming a 50% uptake for trastuzumab and rituximab biosimilars, in 2020 a potential yearly saving of more than 1 million euros may be achieved only in the Messina province (Figure 3). If the uptake of the two biosimilars will stop at 20%, still a yearly potential saving of more than 400,000 euros may be achieved. On the other hand, a wider uptake (80%) may allow a yearly saving or around 1.7 million euros (Figure 3).

Discussion

To our knowledge, this is the first observational study investigating the prevalence of use and the costs of biological drugs in oncology, in a large area from Southern Italy, using administrative healthcare databases.

Our results showed a dramatic increase in biological drugs use in oncology, considering both mAbs and small molecules. These data are in line with the National Report on Medicines use in Italy in 2015 (Osmed 2016), which described a +18.2% increase in mAb consumption (ATC I level: L) in comparison to the previous year. There may be different reasons to explain the increasing number of cancer patients using biological drugs. In the last years, an increasing number of biological drugs have been marketed in Italy, as confirmed by the increasing number of different ATC dispensed in Messina during the study years (from 17 in 2010 to 21 in 2014, data not shown). Furthermore, many biological drugs already approved for cancer treatment gained the extension of the indications of use, thus guaranteeing to a larger number of patients the access to these innovative therapies. We observed an increase in the number of prevalent users over time, despite a decrease in the proportion of incident users (from 61.4% in 2011 to 54.4% in 2014 (data not shown)). These results reflect a growing number of patients taking biological drugs for a longer period of time, rather than initiating the treatment. During the study years, no users of fusion proteins or immunomodulatory agents could be identified. Specifically, concerning aflibercept, the drug use was approved in Sicily since November 2014 and we therefore could not identify any user. Due to their costs, many biological drugs in oncology are included among the top 30 molecules for drug expenditure sustained by public hospitals, being trastuzumab, bevacizumab and rituximab the top three.

Rituximab lost its patent in 2013 and biosimilar is available on the European market since 2017, while biosimilars of trastuzumab and bevacizumab are currently under review by EMA and will probably enter the market in the next future. In USA, bevacizumab biosimilar has been approved in September 2017 (FDA, 2017), rituximab lost its patent in 2016 and the trastuzumab one will expire in 2019 (Rugo et al, 2016).

For the prediction of the expected expenditure until 2020 are the following:

i) Biosimilars are available on the European and Italian market since 2006 and they guarantee a 20-30% lower cost compared to the reference product (Genazzani et al, 2007). Such cost reductions may reach significantly higher percentages where a larger uptake of biosimilars occurs, as demonstrated in Norway with infliximab (Mack, 2015). When originally marketed in Italy, the biosimilars were around 25% cheaper than the corresponding reference products.
ii) Biosimilar rituximab was marketed in Italy in 2017, trastuzumab has lost its patent and the corresponding biosimilar is under review by the EMA, while bevacizumab will lose its patent in 2022, although its biosimilar is already under review by the EMA (Gabi 2015; Gabi 2017).
iii) In recent years, several observational studies evaluated the biosimilars uptake in different Italian Regions, highlighting a relevant heterogeneity across geographic areas (Ingrasciotta et al, 2015; Marcianó et al, 2016). Results showed that the uptake of biosimilars ranged from 25% to 45% for epoetins and from 25% to almost 90% for granulocyte colony stimulating factors, based on the considered Region. This heterogeneity is likely to be due to different healthcare policy interventions promoting the use of the cheapest biological drug and to the skepticism of clinicians regarding the effectiveness and safety of biosimilars.

In 2016, a survey has been conducted in Italy to explore the clinicians' perception on biological drugs and on biosimilars (CittadinanzAttiva, 2017). Most of the interviewed (60%) were rheumatologists,

nephrologists, diabetologists, dermatologists, oncologists, gastroenterologists and endocrinologists. Considering naïve patients, the 27% of the interviewed usually prescribe an originator biological drug. Concerning patients already in treatment with biological drugs, 19% of the clinicians switched the therapy due to non-clinical reasons, i.e., to contribute to the NHS sustainability or to respect specific healthcare policies promoting the use of the cheapest biological drug. Only 28% of the interviewed consider biosimilars as effective and safe as the reference products.

In order to realistically predict the expenditure, we assumed a 25% reduction in the purchase costs of those biological drugs for which the biosimilars are or will be available until 2020 (rituximab and trastuzumab). Considering the observed variability in the biosimilars uptake, we hypothesized four different scenarios assuming an uptake equal to 0%, 20%, 50% or 80% of total amount of the consumption of the two biological drugs, respectively.

Assuming a 50% uptake of the biosimilars only for these two anti-cancer biological drugs, a potential saving of at least € 1million euros yearly in Messina province was hypothesized, thus representing an important strategy to mitigate the constantly increasing expenditure for biological drugs in cancer treatment. The predicted expenditure in scenario n. 1 may be overestimated, due to the potential decrease of the cost of the reference products after the patent expiration. On the other hand, the future marketing of innovative and highly-priced biological drugs for the treatment of cancer will likely increase the pharmaceutical expenditure. In addition, patients firstly treated with the study biological drugs or with the corresponding biosimilars may switch to the new marketed innovative drugs, thus leading to an increase in the total expenditure and to a lower uptake of biosimilars.

Marketing of biosimilars also in oncology may help sustainability of NHS while favoring access to medicines which may have in some cases extremely significant impact on clinical outcomes of cancer patients. In line with this, ipilimumab, trastuzumab emtansine, pertuzumab and brentuximab vedotin have been also identified as innovative drugs by the Italian Drug Agency in light of the documented additional therapeutic value as compared to the available alternative treatments (Italian Medicine Agency, 2017).

In such a context, post-marketing monitoring systems using real world data may allow rapid evaluations of the uptake, appropriate use, safety and economic impact of the highly costly biological drugs and the corresponding biosimilars in cancer patients thus optimizing pharmaceutical expenditure. For most of the biological drugs approved for cancer treatment Italian Drug Agency implemented drug-specific monitoring registries as tools to monitor appropriate use, effectiveness and safety of those drugs which may facilitate post-marketing monitor despite so far these registries have not been systematically used for scientific purposes (Italian Medicine Agency, 2017c). On the other hand an Italian network of claims databases has been successfully built for the post-marketing assessment of benefit-risk profile of biologics/biosimilars in other therapeutic areas thus demonstrating that these sources may offer greater opportunity for exploring clinical and economic impact of biological drugs and related biosimilars also in oncology in real world setting (Ingrasciotta et al, 2015; Marcianó et al, 2016; Ingrasciotta et al, 2016).

Strengths and limitations

Using administrative healthcare databases including dispensing data and hospital discharge diagnosis, this observational study investigated the prevalence of use and the costs of biological drugs in oncology, in a large area from Southern Italy, covering a population of more than 650,000 people.

Using the dispensing databases of the three considered centers, we were able to capture all the dispensing of the study drugs to outpatients resident in Messina area. It is possible that patients resident in Messina receive the study drugs outside the catchment area (i.e., they choose to be treated in other areas of Sicily or in other Italian Regions), but this is rather unlikely. Due to the frequency of the administrations, especially in case of infusion biological drugs, patients are much more likely to choose the closest oncology center.
As administrative databases do not include information about the indication of use, it is therefore possible that, using diagnosis from the hospital discharge database, we detected a diagnosis that is not the main indication for which the drug is used. To minimize the potential misclassification in terms of the indication of use, we considered the last cancer diagnosis within six months prior to the ID as the possible indication of use.

Conclusion

The use and corresponding expenditure of biological drugs for cancer treatment rapidly and dramatically increased almost doubling in 5 years period in a large general population of Southern Italy. Large uptake of biosimilars of trastuzumab and rituximab, which will be shortly available on EU market, may mitigate partly pharmaceutical expenditure of biological drugs in cancer patients. On the other hand, real world data are essential to rapidly monitor benefit-risk profile and appropriate use of biological drugs and related biosimilars in routine care, with the final goal to optimize pharmaceutical expenditure in oncology patients.

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COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflict of interest Gianluca Trifirò coordinates a research team at the University of Messina, which receives research grants for projects that are not related to the topic of the paper. Simona Lucchesi, Ilaria Marcianò, Paolo Panagia, Rosanna Intelisano, Maria Pia Randazzo, Carmela Sgroi, Giuseppe Altavilla, Carmen Santarpia, Vincenzo Adamo, Tindara Franchina, Francesco Ferraù, Paolina Reitano declare that they have no conflicts of interest.

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Ethical Approvals All procedures performed in this study were in accordance with the Ethical Standards of the Institutional Research Committee of the Academic Hospital of Messina (minutes

n.9/2014, 21st July 2014), according to the current national law (8), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
The manuscript does not contain clinical studies and all patients' data were fully anonymised. For this type of study, formal consent is not required.

Table 1. Characteristics of users of biological drugs for cancer treatment in the years 2010-2014 in Messina province

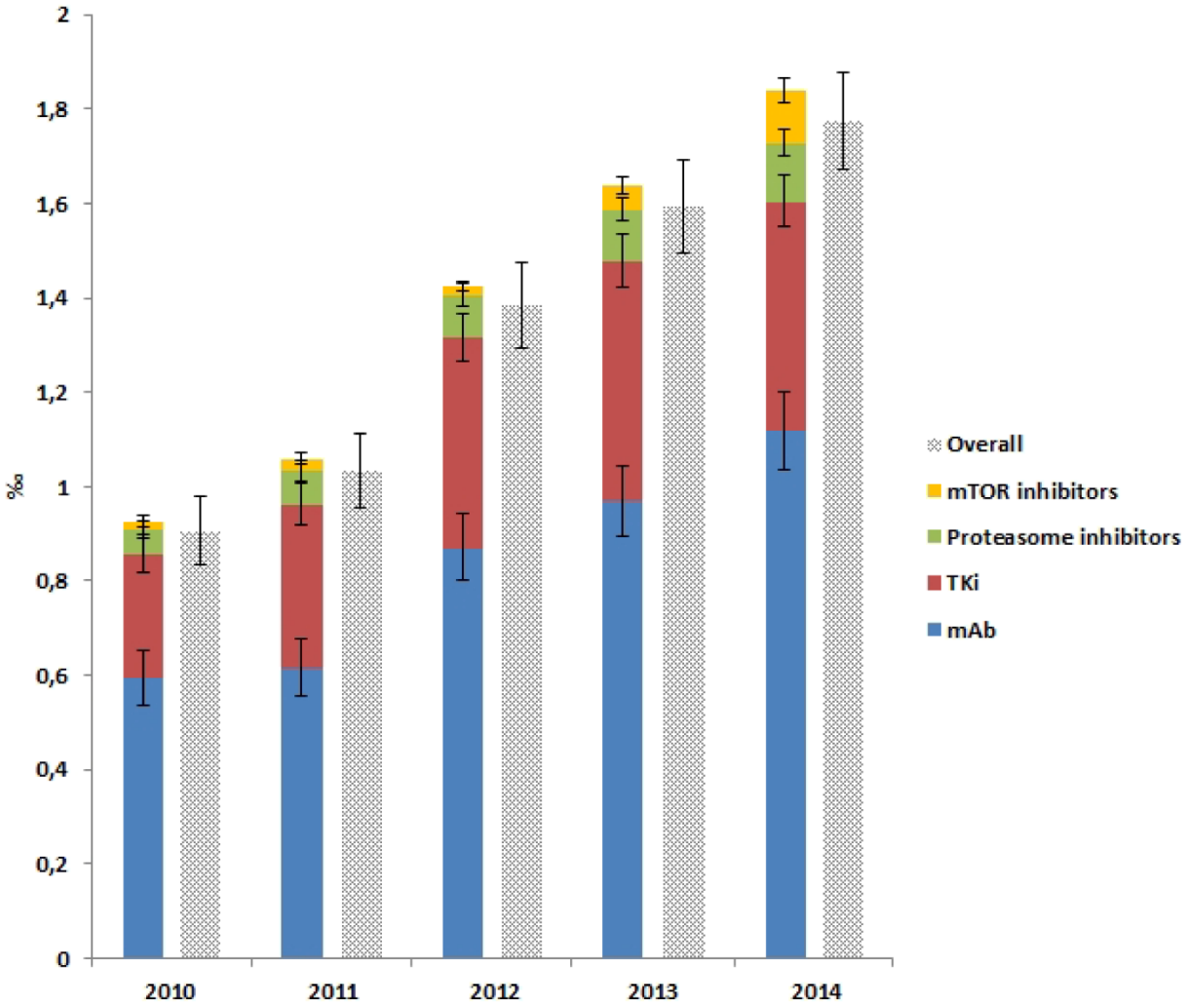
	mAbs N = 1,607	Small molecules				Total N = 2,491
		TKIs N = 609	Proteasome inhibitors N = 203	mTOR-i N = 72	Total N = 884	
Sex						
Male	638 (39.7)	382 (62.7)	95 (46.8)	21 (29.2)	498 (56.3)	1,136 (45.6)
Female	969 (60.3)	227 (37.3)	108 (53.2)	51 (70.8)	386 (43.7)	1,355 (56.4)
Age (years) – median (q1-q3)	**62 (53-71)**	**65 (56-74)**	**70 (61-77)**	**63 (54.5-71.5)**	**67 (58-75)**	**64 (54-72)**
Age categories						
<45	158 (9.8)	44 (7.2)	3 (1.5)	4 (5.6)	51 (5.7)	209 (8.4)
45-64	759 (47.2)	246 (40.4)	60 (29.6)	35 (48.6)	341 (38.6)	1,100 (44.2)
65-79	589 (36.7)	265 (43.5)	113 (55.7)	26 (36.1)	404 (45.7)	993 (39.9)
≥80	101 (6.3)	54 (8.9)	27 (13.3)	7 (9.7)	88 (10.0)	189 (7.5)
Follow-up (days) – median (q1-q3)	327 (130-595)	313 (91-867)	320 (132-644)	225 (69-358.5)	305 (95.5-777)	319 (119-640)
N. dispensing of the biological drug at ID – median (q1-q3)	7 (3-14)	4 (2-12)	16 (8-25)	3 (1-6)	5 (2-16)	6 (3-14)
Type of cancer[a]						
Lymphatic tissue[b]	268 (16.7)	2 (0.3)	3 (1.5)	-	5 (0.6)	273 (11.0)
Breast (female)	220 (13.7)	10 (1.6)	-	4 (5.6)	14 (1.6)	234 (9.4)
Colorectal	148 (9.2)	3 (0.5)	-	-	3 (0.3)	151 (6.1)
Leukemia	77 (4.8)	84 (13.8)	-	-	84 (9.5)	161 (6.5)
Lung	24 (1.5)	79 (13.0)	-	-	79 (8.9)	103 (4.1)
Liver cancer	5 (0.3)	48 (7.9)	-	-	48 (5.4)	53 (2.1)
Multiple myeloma	4 (0.2)	-	116 (57.1)	-	116 (13.1)	120 (4.8)
Metastasis of unspecified primary tumor	389 (24.2)	102 (16.7)	1 (0.5)	8 (11.1)	111 (12.6)	500 (20.1)
Other neoplasm[c]	124 (7.7)	55 (9.0)	14 (6.9)	5 (6.9)	74 (8.4)	198 (7.9)
Previous chemotherapy[d]						
N. of chemotherapeutics						
0	916 (57.0)	517 (84.9)	193 (95.1)	34 (47.2)	744 (84.2)	1,660 (66.6)
1	220 (13.7)	49 (8.0)	9 (4.4)	34 (47.2)	92 (10.4)	312 (12.5)
2-3	422 (26.3)	42 (6.9)	1 (0.5)	4 (5.6)	47 (5.3)	469 (18.9)
≥4	49 (3.0)	1 (0.2)	-	-	1 (0.1)	50 (2.0)
Type of chemotherapeutics						
Cyclophosphamide	342 (21.3)	1 (0.2)	1 (0.5)	-	2 (0.2)	344 (13.8)
Fluorouracil	234 (14.6)	1 (0.2)	-	1 (1.4)	2 (0.2)	236 (9.5)
Doxorubicin	153 (9.5)	-	7 (3.9)	4 (5.6)	11 (1.2)	164 (6.6)
Epirubicin	161 (10.0)	1 (0.2)	-	-	1 (0.1)	162 (6.5)
Docetaxel	128 (8.0)	17 (2.8)	-	2 (2.8)	19 (2.1)	147 (5.9)

Vincristine	99 (6.2)	-	2 (1.0)	-	2 (0.2)	101 (4.1)
Oxaliplatin	71 (4.4)	-	-	1 (1.4)	1 (0.1)	72 (2.9)
Capecitabine	40 (2.5)	14 (2.3)	-	4 (5.6)	18 (2.0)	58 (2.3)
Paclitaxel	51 (3.2)	1 (0.2)		3 (4.2)	4 (0.5)	55 (2.2)
Gemcitabine	12 (0.7)	34 (5.6)	-	2 (2.8)	36 (4.1)	48 (1.9)
Vinorelbine	14 (0.9)	23 (3.8)	-	7 (9.7)	30 (3.4)	44 (1.8)
Carboplatin	17 (1.1)	24 (3.9)	-	1 (1.4)	25 (2.8)	42 (1.7)
Triptorelin	32 (2.0)	5 (0.8)	-	2 (2.8)	7 (0.8)	39 (1.6)
Fulvestrant	19 (1.2)	-	-	10 (13.9)	10 (1.1)	29 (1.2)
Bendamustine	27 (1.7)	-	-	-	-	27 (1.1)
Fludarabine	25 (1.6)	-	-	-	-	25 (1.0)
Others[e]	54 (3.4)	24 (3.9)	2 (1.0)	6 (8.3)	32 (3.6)	86 (3.5)

Legend: mAb= monoclonal antibodies; TKi= tyrosine-kinase inhibitors; mTOR-i= mammalian target of rapamycin inhibitors; q1-q3= interquartile range.
Patients (N= 8) who were dispensed two different drugs at the index date were excluded.
Patients (N= 2) whose sex and age were not available were excluded.
No users of fusion proteins or immunomodulatory agents could be identified during the study years, and these two biological drugs categories were not included in Table 1.

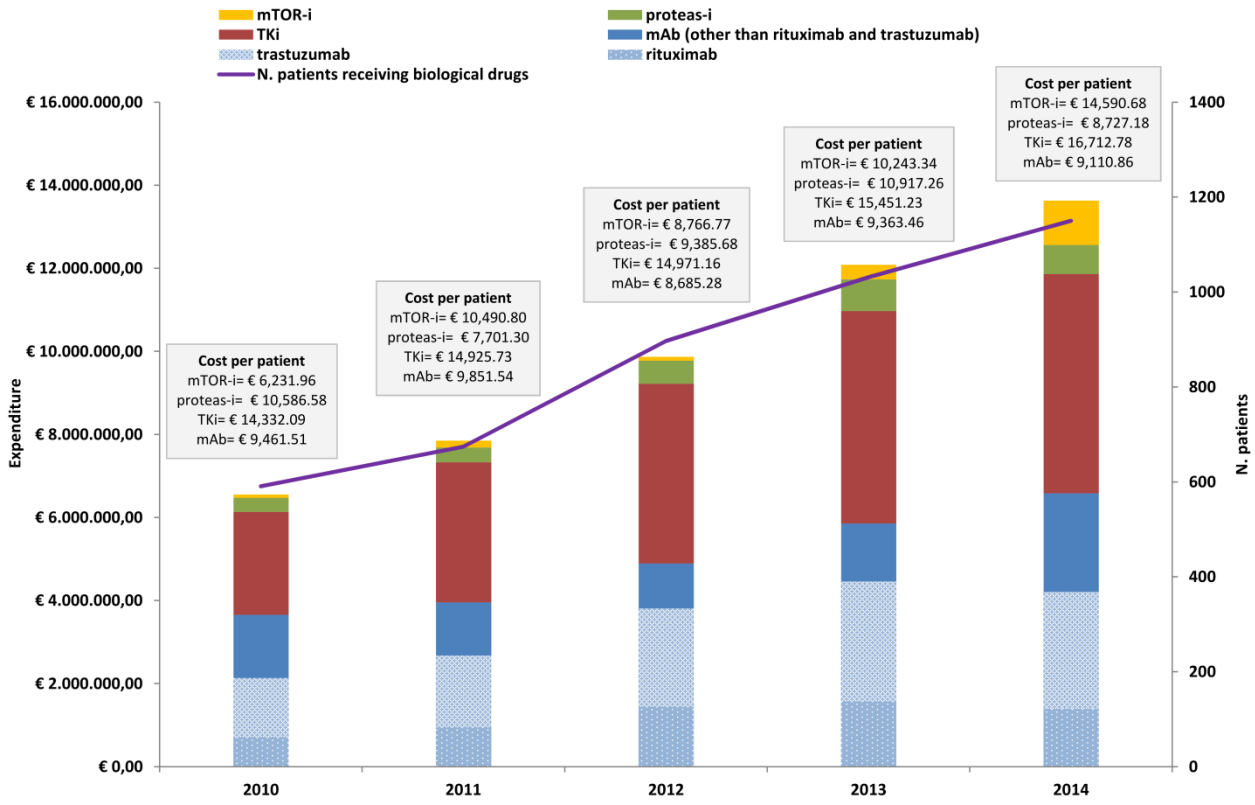
[a] Type of cancer refers to the last cancer diagnosis registered within 6 months prior to the first dispensing of the study drugs, during the study period.
[b] Neoplasms of lymphatic tissue include lymphosarcoma and reticulosarcoma, Hodgkin's disease, non-Hodgkin's lymphoma.
[c] Other neoplasms include neoplasms of peritoneum, eye, brain, thyroid, bones and connective tissue, genitourinary system, pancreas, respiratory organs (other than lungs), skin, carcinomas in situ, monoclonal gammopathy, prostate, benign neoplasm, breast (males), bladder and kidney, esophagus, stomach, duodenum, trachea, larynx, nasal cavities and neoplasms of unspecified nature.
[d] Chemotherapeutics were identified within 6 months prior to the first dispensing of the study drugs, during the study period.
[e] Other chemotherapeutics include cisplatin, pemetrexed, vinblastine, temozolomide, bleomycin, dacarbazine, methotrexate, etoposide, eribulin, topotecan, azacitidine, cabazitaxel, mitoxantrone, tegafur, vindesine, fotemustine.

Fig. 1 Prevalence of biological drugs use for cancer treatment per 1,000 inhabitants, stratified by calendar year



Legend: mAb= monoclonal antibodies; TKi= tyrosine-kinase inhibitors; mTOR inhibitors= mammalian target of rapamycin inhibitors

Fig. 2 Expenditure sustained for the dispensing of biological drugs in oncology in Messina province in the years 2010-2014, stratified by calendar year and type of biological drugs



Legend: mAb= monoclonal antibodies; TKi= tyrosine-kinase inhibitors; mTOR-i= mammalian target of rapamycin inhibitors; proteas-i= proteasome inhibitors.

Fig. 3 Prevision of expenditure for biological drugs for cancer treatment in Messina area, assuming an uptake of trastuzumab and rituximab biosimilars of 0-20-50-80%

Table S1. Biological drugs for cancer treatment available on the market, in the study period.

ATC	Brand name	Active substance	Type of biologic	Indication for use	Biological target	AIFA postmarketing registry	Innovative drugs
L01XC02	Mabthera	Rituximab	MAB	-NHL -CLL -Rheumatoid arthritis -Granulomatosis with polyangitis	CD20	Available for NHL, from 05/10/2009	
L01XC03	Herceptin	Trastuzumab	MAB	-Breast cancer (early and metastatic) - Metastatic gastric cancer	HER2	For metastatic gastric cancer available from 14/01/2011	
L01XC04	Mabcampath	Alemtuzumab	MAB	-CLL	CD52	CLL	
L01XC05	Mylotarg	Gemtuzumab	MAB	-AML	CD33 positive		
L01XC06	Erbitux	Cetuximab	MAB	- mCRC -Head and neck cancer (Advanced, recurrent or metastatic)	EGFR(HER1/ERBB1) (Kras wild type)	For mCRC Available from 02/10/2008 ; For head and neck available from 23/12/2010	
L01XC07	Avastin	Bevacizumab	MAB	-mCRC -Breast Cancer (metastatic) -NSCLC (advanced, metastatic or recurrent) -RCC (advanced or metastatic) -Ovarian (advanced or recurrent) cancer -Fallopian tube (advanced or recurrent) cancer	VEGFR	For mCRC available from 11/10/2005 ; -For breast Cancer, NSCLC and RCC available from 09/07/2008 ; For ovarian, fallopian tube and peritoneal cancer available	

				-Cervical (persistent, recurrent or metastatic) cancer -Peritoneal (advanced or recurrent) cancer		from 07/01/2014	
L01XC08	Vectibix	Panitumumab	MAB	-mCRC	EGFR (Kras wild type)	Available from 17/01/2009	
L01XC09	Removab	Catumaxomab	MAB	-Malignant ascites	Epcam positive carcinomas	Available from 10/10/2011	
L01XC10	Arzerra	Ofatumumab	MAB	-CLL	CD20	Available from 14/06/2011	
L01XC11	Yervoy	Ipilimumab	MAB	-Melanoma (unresectable or metastatic)	CTLA4	Available from 09/03/2013	Important
L01XC12	Adcetris	Brentuximab vedotin	MAB	-HL (relapsed or refractory) -ALCL (relapsed or refractory)	CD30	HL available from 08/07/2014	Potential
L01XC13	Perjeta	Pertuzumab	MAB	-Breast Cancer (metastatic or neoadjuvant)	HER2	Available from 08/07/2014	Important
L01XC14	Kadcyla	Trastuzumab emtansine	MAB	-Breast Cancer (unresectable, advanced or metastatic)	HER2	Available from 11/10/2014	Potential
L01XC15	Gazyvaro	Obinutuzumab	MAB	-CLL -FL	CD20		
L01XE01	Glivec	Imatinib	TKI	-GIST (unresectable or metastatic) - Dermatofibrosarcoma protuberans (recurrent or metastatic) - Myelodysplastic / myeloproliferative disease - Advanced hypereosynotype syndrome (HES) and / or chronic	PDGF E SCF		

				eosinophilic leukemia (LEC) - ALL (Ph+) - CML (Ph+)			
L01XE02	Iressa	Gefitinib	TKI	-NSCLC (advanced or metastatic)	EGFR	Available from 11/06/2010	
L01XE03	Tarceva	Erlotinib	TKI	-NSCLC (advanced or metastatic) -Pancreatic Cancer (metastatic)	EGFR	NSCLC from 28/07/2006	
L01XE04	Sutent	Sunitinib	TKI	-GIST(unresectable or metastatic) -mRCC (advanced or metastatic) -pNET (unresectable or metastatic)	PDGFR E VEGFR	mRCC from 04/10/2007	
L01XE05	Nexavar	Sorafenib	TKI	-Hepatocellular Carcinoma -RCC -Thyroid Carcinoma (advanced or metastatic)	VEGFR, PDGFR, KIT E RAF	For hepatocellular carcinoma available from 09/07/2008 ; -For RCC from 23/11/2006	
L01XE06	Sprycel	Dasatinib	TKI	-CML (Ph+) -ALL (Ph+)	HER2(ERB2/neu), EGFR(HER1/ERBB1)	For all indications available from 26/05/2007	
L01XE07	Tyverb	Lapatinib	TKI	-Breast Cancer (advanced or metastatic)	EGFR(HER1/ERBB1), HER2 (ERB2/neu)	Available from 03/06/2009	
L01XE08	Tasigna	Nilotinib	TKI	-CML (Ph+)	ABL	Available from 08/08/2008	
L01XE09	Torisel	Temsirolimus	mTOR inhibitors	-Renal Cell Carcinoma (advanced) -Mantle cell lymphoma (relapsed or refractory)	mTor	For RCC available from 07/10/2008 ; For mantle cell lymphoma	

						available from 25/08/2011	
L01XE11	Votrient	Pazopanib	TKI	-RCC (first line or advanced) -Soft tissue sarcoma	VEGFR, PDGFR e KIT	Available for RCC, from 21/05/2011	
L01XE13	Giotrif	Afatinib	TKI	-NSCLC (Advanced or metastatic) -NSCLC (Advanced or metastatic) squamous histology	EGFR (HER1/ERB1) e HER2(ERBB2/neu)	Available from 24/12/2014	
L01XE14	Bosulif	Bosutinib	TKI	-CML (Ph+)	ABL	Available from 01/10/2014	
L01XE16	Xalkori	Crizotinib	TKI	-NSCLC (advanced)	ALK, MET e ROS1 (ALK deletion or ROS1 gene alteration)	Available from 24/04/2013	
L01XE17	Inlyta	Axitinib	TKI	-RCC (advanced)	KIT, PDGFRβ, VEGFR1/2/3	Available from 05/01/2014	
L01XE18	Jakavi	Ruxolitinib	TKI	-Myelofibrosis -Polycythaemia vera	JAK1/2	Available from 14/10/2014	
L01XE24	Iclusig	Ponatinib	TKI	-CML -ALL (Ph+)	ABL, FGFR1-3, FLT3, VEGFR2 (T315I mutation)	Available for all indications from 25/12/2014	
L01XE25	Mekinist	Trametinib	TKI	-Melanoma (unresectable or metastatic)	MEK (BRAF V600 mutation)		
L01XX32	Velcade	Bortezomib	Proteasome inhibitors	-MM -Mantel Cell Lymphoma	PROTEOSOME	-For MM available from 23/07/2009	
L01XX44	Zaltrap	Aflibercept	VEGFR-Trap	-mCRC	PIGF, VEGFA/B	Available from 11/10/2014	
L03AC01	Proleukin	Aldesleuchin	Immunomodulatory agent	-Renal metastatic cancer			
M05BX04	Xgeva	Denosumab	MAB	-Bone metastases from solid tumor	RANKL	Bone metastases from solid tumor	

				-Giant cell tumor of the bone (unresectable)			
V10XX02	Zevalin	Ibritumomab tiuxetano	TKI	-Follicular lymphoma -NHL (relapsed or refractory)	CD20	Available for follicular lymphoma, from 19/06/2005	

Legend: ATC= Anatomic Therapeutic Chemical classification system; TKI= Tyrosine kinase inhibitor; MAB= Monoclonal antibody; MTD= medullary thyroid carcinoma; NHL= Non Hodgkin's Lymphoma; HL= Hodgkin's Lymphoma; ALL= Acute Lymphoblastic leukemia; ALCL= Anaplastic Large Cell Lymphoma; CML = Chronic Mielogenous Leukemia; AML= Acute Myeloid Leukemia; CLL= Chronic lymphocytic leukemia; NSCLC= Non small Cell Lung Cancer; GIST = Gastrointestinal Stromal Tumor; RCC= Renal Cell Carcinoma; MRCC= Metastatic Renal Cell Cancer; MDT= Medullary Thyroid Cancer; MM=Myeloma multiple; mCRC= Metastatic colorectal; AIFA= Italian medicine agency

Table S2. Lower and upper bounds of 95% Confidence Intervals of prevalence of study drugs use, stratified by type of drug and calendar year.

	95% Confidence Intervals bounds									
	mAb		TKi		Proteasome inhibitors		mTOR inhibitors		Overall	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
2010	0,0561	0,0620	0,0366	0,0425	0,0143	0,0201	0,0079	0,0137	0,0700	0,0758
2011	0,0572	0,0631	0,0422	0,0481	0,0176	0,0235	0,0094	0,0153	0,0749	0,0808
2012	0,0688	0,0747	0,0484	0,0543	0,0204	0,0263	0,0075	0,0134	0,0874	0,0933
2013	0,0727	0,0786	0,0521	0,0581	0,0225	0,0284	0,0149	0,0208	0,0941	0,1000
2014	0,0783	0,0842	0,0508	0,0568	0,0242	0,0302	0,0230	0,0290	0,0995	0,1054

Legend: mAB= monoclonal antibodies, TKi= tyrosine-kinase inhibitors; mTOR= mammalian target of rapamycin.

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5. General discussion

Biological drugs in oncology are increasingly used in clinical practice, that have an important impact on health outcomes as well as expenditure. Most of the newly approved drugs in Italy during 2013-2016 years were highly costly medicines, contributing significantly to the increase in pharmaceutical expenditure. In particular, drugs for cancer were estimated to account for a pharmaceutical expenditure of over half a billion Euros only during the first year of treatment in Sicily. Given this extremely high cost, it is essential to employ strategies to maximise the benefits and contain the costs of biologic drugs. There are at least two such strategies: promote biosimilar use and replace biological drugs with biosimilars, and increase the appropriateness of biologic and biosimilar drug use through monitoring. Adult studies have been conducted to assess the prevalence and comparative effectiveness of biosimilar and biological, and such studies should be done in children (Ingrasciotta et al, 2016).

Another important role of big data is to confirm findings obtained from clinical trials, which may not reflect clinical practice. According to Davis C. et al, after a median follow-up of 5.4 years on 48 cancer medicines approved by EMA for 68 indications, from 2009 to 2013, only 35 (51%) indications have led to a significant increase in survival or an increase in quality of life, while for 33 (49%) indications the data derived are uncertain (Davis et al, 2017). Real world data could therefore be a valid tool to monitoring approved drugs and to demonstrate or to disprove findings obtained from clinical trials in actual clinical practice. The use of biologic drugs in a pediatric oncologic setting is an area which requires more attention. Currently used biologic drugs in pediatric patients are often used based on safety and efficacy data that has been extrapolated from adult data. The present thesis showed that there is quite a large number of trials in the pediatric setting concerning biological drugs.

6. Conclusion

The use of biologic drugs is a growing trend and could represent a problem for Italian national healthcare system because of high costs, so it's important to implement strategies to maximise benefits and contain costs, for example using biosimilar drugs in clinical practice, may moderate pharmaceutical expenditure of biological drugs in cancer patients. Future work needs to address the need of special populations, such as children but also elderly persons. Real world data could be useful to monitor approved drugs in order to demonstrate or to disprove the data obtained from clinical trials and would more information on the use and costs of biological and biosimilar drugs in oncology, especially in special populations.

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