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POINT OF VIEW

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Improving the management of high cost anticancer drugs in a health care system

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ABSTRACT

As a consequence of the rise in cancer prevalence and in the cost of anticancer drugs, global spending for cancer is increasing rapidly. The aim of this work is to identify and assess some effective cost management parameters and possible strategies to contain expenditure. Cost limitation could be achieved by implementing effective prevention measures and other main actions: diffusion of tailored therapies; systematic postmarketing reviews; cost-effectiveness assessment; accurate treatment choices; more transparent and effective managed entry agreement policies; waste management through personalized dose preparation. To better manage high cost anticancer drugs, oncologists and hospital pharmacists should collaborate in choosing the right drug, for the right patient, at the right time. In addition, besides promoting the use of biosimilars and generic drugs, when different products have a similar clinical effectiveness, a cost-minimization analysis should be performed to identify the best clinical approach at the lowest cost. With the same purpose, verifying real life outcomes by managing postmarketing analyses helps to renegotiate price agreements in a value-for-money model; this could be arranged if the regulatory agencies renegotiate the previously established price within a defined time period. Finally, the centralization of high-cost drug preparation and the implementation of a drug-day (vial sharing) will reduce drug waste.

Keywords: Drug expenditure, Managed entry agreement, Oncology, Preparation waste, Postmarketing register

Introduction

In 2012, the World Health Organization (WHO) reported 14.1 million cancer diagnoses, 8.2 million cancer deaths and 32.6 million people living with cancer (within five years of diagnosis) worldwide (1). As a consequence of the increasing cancer burden, the curve of global spending on cancer medicines has rapidly increased. In 2014, this reached a value of about $100 billion/year compared to about $75 billion/year five years earlier, and cancer care costs are expected to increase from $125 billion in 2010 to $158 billion in 2020 (2). The cancer related market has increased despite the worldwide economic crisis of recent years, with seemingly high profits in Western countries. In addition, the approval of new biologic drugs and the boost of cancer immunotherapies, especially if used in combination, are expected to further increase the pharmaceutical expenditure for cancer management over the next few years (3). The aim of this review is to identify the elements of healthcare management involved in high-cost cancer-drug settings and the possible strategies to strictly control cancer-related expenditure by assessing these elements. The following considerations regard both clinical aspects and economic policies influencing health systems; the analysis is performed from the point of view of the public health system, in particular of the hospital pharmacist.

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Primary prevention measures in oncology

The first step towards limitation of capital expenditure in a health system is to implement an effective primary prevention program. Primary prevention measures are considered to give the greatest economic return in both cancer and other disease management. On this basis, many European countries are investing a substantial portion of the gross domestic product (GDP) in prevention; Italy, however, invested only 0.5% of its GDP in 2012 (4). The importance of prevention in the oncological setting is strongly supported by many examples. First of all, the promotion of a healthier life style is a key component in an effective prevention strategy (5, 6). Obesity is considered to be a global health problem, affecting people of all ages. Excess body mass is a known risk factor for many diseases, including several cancers (colorectum, pancreas, gallbladder, oesophagus adenocarcinoma, kidney, endometrium, and postmenopausal breast cancer); it was shown that being obese or very overweight during adolescence may double the risk of developing colorectal cancer in middle-age

(7, 8). Moreover, a wiser use of vaccines is also considered an effective prevention tool (9, 10). Human papillomavirus vaccination has been demonstrated to be cost-effective for the prevention of both cervical and oropharyngeal cancer (11-13). Furthermore, some authors sustain that the use of low-dose ASA may provide modest cancer mortality benefits in cardiovascular primary prevention populations (but effects are not clearly established since current estimates are imprecise and relatively unstable) (14). Thus, cancer prevention should not be carried out exclusively through screening programs, some of which are known to be of dubious value (e.g. prostate cancer screening for PSA (15, 16)), but also through promoting treatment and lifestyle changes able to reduce disease progression or hospitalization and surgery.

Tailored therapies

In the dynamic scenario of cancer pharmacology, oncologists and hospital pharmacists should collaborate in order to choose the right drug, for the right patient, at the right time (17). Efficient guideline implementation is important to drive clinicians to choose the best treatment for each stage of each different tumor type, to avoid prescriptions of new brand drugs in clinical cases that can be managed by traditional treatment approaches. Along this line, the American Society of Clinical Oncology (ASCO) has recently published a guidance statement to provide value-based treatment (18). In context, the use of tailored therapies in oncology has spread over the last few years, having markedly changed the outcomes for some diseases, and raised new questions on cancer treatment tailoring. Genetic tests in clinical diagnosis are determinant in choosing the most (cost-)effective drugs for prevention or treatment of targeted patient groups. These therapies mainly include monoclonal antibodies and small molecule inhibitors. In addition, personalization of therapy had a relevant impact on the assessment of drug effectiveness and toxicity, and the economics of cancer care. However, targeted therapy is often added to, rather than replace traditional chemotherapy. If the added therapy is a monoclonal antibody, costs can escalate exponentially (19). For example, many targeted therapies, which were initially intended for treatment of metastatic disease, have recently been extended to the adjuvant setting (20). On one hand, this approach can produce a significant delay in cancer progression; on the other hand, in aggressive cancers where palliative treatment is preferred, inadequate results may be achieved. A good example would be metastatic non–small-cell lung cancer, in which early palliative care leads to significant improvements in quality of life, further mild treatment and longer survival (21). In the metastatic setting, the combination of different therapies is a standard approach to delay progression and inhibit resistance. On the other hand, the addition of targeted drugs to standard chemotherapy is not always the best cost-effective choice. It is a common practice to associate a monoclonal antibody, such as bevacizumab, with traditional chemotherapy in colorectal cancer. However, a meta-regression study, carried out from 2000 to 2012, which analyzed the development of treatment in RCTs on colon-rectal cancer (22) showed only a slight improvement in overall survival, and just a small incremental advantage in subgroups receiving bevacizumab. A small increase in efficacy, in this case, does not justify the high drug cost.

Use of biosimilars

The encouraged use of generic and biosimilar drugs in clinical practice is another factor expected to enhance savings. Indeed, the main reason to use generics and biosimilars is cost reduction, considering their comparable/similar efficacy and safety but lower cost compared to the original drug. It is estimated that in the next five years, 20 biologic drug patents (e.g. rituximab, trastuzumab, bevacizumab) will expire and this could generate savings of more than $300 million in Europe alone (23), given that biosimilar prices are generally 20% to 35% lower than the price of the reference product (24). In addition, these savings could support costs of new innovative drugs, improving health outcomes. According to another study (25), about 1.6 billion Euros per year could be saved in the EU if biosimilars would successfully replace the reference product. However, in many countries, doctors are cautious in prescribing these drugs. Hence, it is important to spread the knowledge that biosimilars have equal efficacy and quality ratio as other drugs, and undergo the same controls as originators for registration.

Postmarketing analysis

As a consequence of the need for the management of anticancer drug cost “explosion”, postmarketing assessments are becoming more and more relevant and this is true especially for new drugs. Since the cost of cancer management is driven by drug cost, supportive care, inpatient facilities and social costs, Health Technology Assessment (HTA) should be used more often. HTA, aiming mainly to compare the value of relevant alternatives, must include evaluation of effectiveness, safety, cost, social and ethical aspects. In particular, pharmacoeconomics is a necessary tool to allocate healthcare resources in a fair and rational way, a key guide for managing new oncology drug use and price negotiation (26). In the field of oncology, several cost-effectiveness studies can be cited: for example a recent article regarding denosumab used in patients with castration-resistant prostate cancer (27). When two products have a similar clinical effectiveness, a cost-minimization analysis should be performed to identify the best clinical approach at the lowest cost. Unfortunately, the main obstacle to HTA studies is the lack of information on new drugs at the time of market approval. If available data are inadequate to conduct a solid study, then the time needed to collect solid data on efficacy and cost can delay the availability of the new drug. Recent reports indicate that clinical oncologists feel the need to find a consensus on what is worth paying for, and ask for transparent, independent government research on comparative effectiveness of cancer drugs (28, 29). This can only be achieved with postmarketing evaluations, when more information has become available from clinical practice. In conclusion, these postmarketing analyses are excellent strategies to verify real life outcomes and real sample size with the aim to renegotiate price agreements using a value-based pricing method. This could be done if stakeholders, during the approval and reimbursement

process, gree to revise, over a defined period of time, the previous negotiated price.

Managed entry agreements

The main crucial factor that helps to control the public drug expenditure is drug price negotiation between stakeholders (drug manufacturer and regulatory agencies), not only at the time of market approval but also after an adequate period of drug utilization in real life conditions. Postmarketing registries, established by the Italian Medicines Agency in 2005, represent an example of a national application of an automated workflow handling the personalized drug distribution in hospital pharmacies and local public pharmaceutical services, with the intent of both improving the postmarketing effectiveness analysis and closely monitoring the clinical activity as well as implementing the managed entry agreements (MEAs) (30). The AIFA registry is an extensive electronic medical record platform shared by thousands of doctors and pharmacists, where patient data are recorded for the majority of cancer drugs used, such as monoclonal antibodies and tyrosine kinase inhibitors.

In fact, the management of drugs with high socio-economic impact is managed in Italy within those web-based registries by reimbursement procedures and, in this process, the role of the hospital pharmacist is crucial (31). The main aim of the AIFA register is to check the efficacy, appropriateness and safety of drugs used in real life, in order to reduce the risk for payers to reimburse technologies that could result less cost-effective than expected at the time of market approval, and, at the same time, to allow drug manufacturers to obtain a quicker market access. MEAs include different types of contracts that aim at limiting drug expenditure by applying a price rebate based on the observed performance in real life clinical conditions. Thus, purchasers and manufactures will be forced, over time, towards transparency in decision making.

Roughly, different types of MEA contracts are possible. The most utilized in Italy are: a) Performance-Based Risk Sharing schemes, mainly the so-called Payment-by-Results, where the producer reimburses for those patients who do not respond to a specific treatment; b) Financial-Based schemes, mainly the Cost-Sharing agreement, where a discount is allowed on the first cycles of therapy; or the Capping agreement, where the manufacturer pays back the cost of the drug when this is prescribed in quantities higher than agreed (32).

Payment-by-Result is becoming the preferred type of agreement in Italy. However, it might deserve some criticism:

- the management of this MEA is very difficult as it is entirely based on registries. According to the 2015 OSMED Report (33), something less than 29.000 clinicians and 2000 pharmacists are at present involved in the management of 138 registries, where data from more than 700.000 patients are stored. As far as we know, the full management costs of these registries have not been evaluated as yet (the direct cost of this registry management is considered to be around €1 million (34) but this amount might be underestimated);
- the market-access agreements can be considered a way for manufacturers to keep official prices in Italy at the same high level of other countries in Europe (31);
- it is worth noting that the real payback revenues obtained from this mechanism in the past (at least until 2013) do not seem to exhibit high figures. The situation may have improved since then, but there is a lack of comprehensive and analytical data. For example, the incidence of payback on the expenditure for the drug involved is unknown.

In principle, the register is a useful tool because it could provide epidemiological indications, while allowing the calculation of the amount of payback, in case of treatment failure, from the pharmaceutical firm. Hence, the register has a valuable cohort potential for postmarketing studies acting in a similar way to "conditional drug approval", identifying patients who experience major benefits and less toxicity (35). However, the main current problem is that data are not accessible publicly, thus a transparent nationwide value-based evaluation of cancer treatments is, unfortunately, not possible.

Furthermore, it may be worth mentioning that, in some European countries, the well-known value-based pricing (VBP) system is applied. VBP refers to the reimbursement negotiation of pharmaceuticals based on their therapeutic value. In Italy, drug reimbursement is currently managed through a mixed approach where VBP is only one of the several parameters taken into account in the negotiation. Higher control of the expenditure for anti-cancer agents could be reached integrating reimbursement negotiation with post-marketing patient-based national registries that provide rebates based on a more efficient management of MEA.

Drug waste savings

Last, but not least, an excellent way to optimize cancer related costs is through the correct management of expensive drugs within a hospital pharmacy. In particular, two main actions that could be undertaken to achieve this aim are: centralization of drug preparation and implementation of a drug-day (vial sharing) (35). These methods allow the reduction of waste while dose personalization, which is a basic requirement for oncology drugs, remains unaltered. This approach is applied in well-organized oncology institutes. An example can be the case of the monoclonal antibody ipilimumab, which is a high cost drug used in advanced or metastatic melanoma. Given that this type of cancer is relatively rare, when the tailored treatment is prepared in small oncology centers, drug waste is unavoidable. The Veneto Institute of Oncology (IOV), with a resident population of 4 million, is a regional center for melanoma. In this hospital, both prescriptions and preparations are performed in centralized recurring single "drug-days", thus cutting out drug waste. At IOV, this approach was calculated to save more than 10% of the total value of the treatment (36).

Conclusions

The cost of cancer management is considered to be a leading global healthcare expenditure and, as seen in recent years, it is increasing. Therefore, to obtain sustainability for the national health service (NHS), drastic actions are required. The boost of drug costs is partly due to the introduction of new more expensive drugs such as those used in targeted

therapies and immunotherapies. In addition, the management of costs can only be achieved by a unanimous cooperation between the different public healthcare stakeholders: oncologists, clinical pharmacists, nurses etc. The containment of costs will result from: wiser prescriptions by clinicians; HTA and economic evaluations by national and local agencies; systematic reviews on the drug postmarketing effectiveness and toxicities, in order to renegotiate prices on a real health value basis; greater use of biosimilar and generic drugs; increased efficiency in the process of drug prescription and preparation.

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