

The role of generic medicines and biosimilars in oncology in low-income countries

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Cancer cases are rising in developing countries which are already grappling with high levels of infectious diseases including human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB) and malaria. The United Nations (UN) including the World Health Organisation (WHO) have called on member states to establish strategies to deal with the increasing burden of non-communicable diseases, including cancer, in developing countries. The complexity of cancer care and management calls for innovative approaches in low resource settings especially since these settings are already grappling with huge challenges in healthcare including lack of funds, weak human resource base and lack of treatment guidelines. Whilst the cost of medications is by no means the only high cost in cancer care, the availability of affordable anti-cancer generic drugs and biologically similar therapeutic agents (biosimilars) will go a long way to reduce overall cost of cancer care. The high cost of anticancer medicines has been cited among the reasons whilst patients default in treatment. Non-proprietary anti-cancer agents – generics and biosimilars – often cost several times lower than their innovator branded counterparts. They can reduce the cost of care significantly and their multi-source origin often provide guarantee in supply. The use of generic and biosimilar products is hinged on the assumption that they are of assured quality and of the same pharmaceutical integrity as their innovator counterparts. The use of these products however is associated with challenges that must be understood and addressed. The quality of all generics and biosimilars should be rigorously controlled and assured. Measures to prevent counterfeit and sub-standard generics and biosimilars should be developed and the cold-chain must be maintained for all biosimilars. In addition to these, the WHO is encouraged to develop a prequalification scheme to assist countries without strong regulatory systems to procure anticancer generics and biosimilars of assured quality

introduction

Cancer accounts for around 15% of all deaths globally per year, equating to around eight million people in 2010 alone [1]. This is greater than the combined number of deaths from human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB) and malaria. Although the world is rightly focused on controlling the spread of acute diseases such as these, a matter of great concern is the lack of focus on cancer—a chronic disease—which is a great source of suffering in developing nations such as those in Africa, where resources for treatment and prevention are limited or non-existent. In 2010, the United Nations (UN) passed a resolution on non-communicable diseases [2] leading eventually to a UN high level summit on non-communicable diseases in New York, USA, in 2011 [3]. The NCDs of interest include cardiovascular diseases, diabetes and cancer and several. While several proposals were made to control these diseases, the sheer complexities of cancer care requires more focused and dedicated attention if progress

were to be achieved quickly, especially in low-income regions including Africa. In addition to shortage of skilled manpower for cancer care, issues of diagnostics and cost play huge roles especially since governments are unable to fund cancer care adequately. For most patients, the cost of medicines is a huge barrier to adequate cancer care. Any significant reduction in the cost of medicines will therefore inure to the benefit of patients who often have to pay out-of-pocket for cancer care. This article examines the role of generics and biosimilars in oncology in low-income countries with the view of highlighting the potential benefits that may be derived from these while discussing the challenges that the use of these products may bring.

challenges facing cancer control in Africa

- (i) High levels of communicable disease, especially HIV/AIDS, TB and malaria, so cancer not a priority [4]
- (ii) Fragmented and underfinanced health care systems that have not been oriented towards non-communicable disease management [4]
- (iii) Significant lack of cancer incidence and prevalence data due to lack of cancer registries

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- (iv) A lack of cancer awareness, knowledge and capacity amongst health workers [5]
- (v) Lack of screening, diagnostic and treatment facilities
- (vi) Lack of access to life-extending therapies and palliative care.

potential solutions to improve cancer control

- (i) Extensive investment to support improvements in infrastructure and equipment [4]
- (ii) Resources to implement cancer surveillance, detection, prevention, diagnosis, treatment and palliative care programmes [5]
- (iii) Education and training for existing and new healthcare workers
- (iv) Access to up-to-date medical literature from a range of top peer-reviewed journals
- (v) Research collaborations with developed countries [6]
- (vi) Awareness raising campaigns about cancer [6]
- (vii) Access to drugs and vaccines at affordable prices [6].

If we focus on the delivery of cancer care, we need to understand why patients in Africa have such poor survival. There are sporadic studies from Africa detailing specific examples of differential treatment outcomes when comparing survival with Western centres. A recent report on the results of nephroblastoma treatment in Nigeria [7] is summarised as follows:

- (i) Forty-two patients with a histologically confirmed nephroblastoma presenting serially to a single-specialist centre had a 5-year survival rate of 38% (this compares with western survival rates of 85%)
- (ii) Late presentation: clearly stage at presentation has a large effect on the outcome and there are several proposed reasons underpinning the preponderance of stage IV patients; late referral; lack of awareness in the general population and in health professionals; delayed recourse to orthodox medicine after traditional practitioners and prayer houses have failed
- (iii) Resource deficiency: five patients could not afford chemotherapeutic drugs and operation was delayed on seven children because they could not afford blood and antibiotics. Poverty was largely responsible for default from treatment
- (iv) Poor compliance with the treatment regimen: 17 children could not comply as cytotoxic drugs were given only when available
- (v) Lack of collaboration/referral/multidisciplinary working among clinical community

Clearly, limited access to potentially curative chemotherapy played a major role here, underlining the importance of availability of affordable drugs of assured quality. This makes the case for generics and biosimilars strong, even though there are challenges in the use of these medicines as well.

According to the US Food and Drug Administration, a generic drug 'is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and

intended use' [8] The same definition is adopted by national drug regulatory agencies worldwide with minor variations. Generics are expected to have the same active ingredients as branded or innovator products. Similar biological products or biosimilars are the 'generic versions' of biological substances and are regulated as such with national agencies including the European Medicines Agency providing clear definitions and guidelines on their use (see for example CHMP/437/04 [9]). Strictly speaking, biosimilars are not generic medicines since there are subtle and therapeutically significant differences between biological products arising out of several sources, including the manufacturing process and choice/source of seed material. The term 'generic medicines' or 'generics' therefore tends to be reserved for chemical (usually small molecular size) entities, while the term 'biosimilars' are reserved for the non-innovator versions of similar biological substances. In the main, generics are supposed to have the same bioavailability and/or bioequivalence as the innovator products, and there are strict rules on the regulation of generics in most advanced countries. In the case of biosimilars, it is accepted that two biosimilar products are not identical due to differences in the cell lines, manufacturing process, persistence of residues or other factors linked to the cell line or production process. Both generics and biosimilars are used in healthcare with the expectation that they deliver the same therapeutic benefit as the innovator products they are trying to mimic. However, there are cases where generics and biosimilars have not yielded the expected therapeutic outcomes due to several factors.

In low-income countries, regulation of all pharmaceuticals including generics and biosimilars is variable with some settings having no standards at all and hence unable to properly regulate these products and others having world class standards. The challenges of generics and biosimilars used in oncology in terms of quality assurance and control are many and numerous and developed countries are just beginning to develop the framework for their control (as described elsewhere in this supplement).

Generics and biosimilars play a huge role in expanding access to medicines especially in relation to cost of products (they are supposed to be cheaper than innovator products), availability and access. The concerns raised about them relate usually to their quality and pharmaceutical integrity.

In oncology where products are highly specialised and very expensive, generics and biosimilars do play a role in all countries. However, there is very little published information on the benefits or risks associated with the use of generics and biosimilars in oncology in all settings in general and almost no publication on the role of generics and biosimilars in developing countries. This review examines the role of generics and biosimilars in low-income countries using Ghana as an example. It looks at the potential benefits of generic and biosimilar oncology medicines and explores the challenges that may be associated with the use of generics in this critical area. It discusses options countries and healthcare facilities may explore and makes recommendations for proper regulation of generic and biosimilar oncology products while calling for special quality and safety monitoring of these products and a rigorous examination of their effectiveness in real-life settings.

cancer care in low-income countries

Cancer care in developing countries is hampered by several factors including the absence of appropriately trained healthcare professionals, lack of diagnostic equipment, high cost of medications and little or no reimbursement of oncology care in healthcare financing schemes. The cost of medicines, by no means the only or main cost to cancer patients, can however be significant, and the use of generics and biosimilars can significantly lower the cost of patient management. For example, the average cost of the most common generics used in Ghana is several folds lower than that of branded products (Table 1). In some cases, the branded products are six or more times the cost of generics. This cost comparison undertaken in Ghana is broadly applicable in most of sub-Saharan Africa and gets even worse in countries where the supply chain is weaker. In fact, Ghana is often considered among the 'better performing' countries and the situation elsewhere is expected to be similar or more dire (this excludes the Republic of South Africa which is much more modern with more human, technical and financial resources). With such huge differences between the cost of generic and branded products, it is obvious that resort to generic medicines will provide huge financial benefits to both patients and the healthcare system. These savings increase by orders of magnitude when biosimilars are involved though in the survey in Ghana (Table 1), there were no biosimilars circulating in trade, obviously due to the high cost of the products and the low demand for biosimilar anticancer

agents in view of cost. While generics and biosimilars provide huge savings financially, their use is not without challenges and, to ensure that these products retain favourable benefit-risk profiles, it is essential to appreciate and mitigate the risks that may be associated with them.

the case for generics:

- (i) Cost—most of the oncology medicines used in Ghana are generics because of cost! Reimbursement of the few products that are eligible for reimbursement under the National Health Insurance Scheme is based on the median generic price forcing dispensers to seek and dispense only generics. Several products are not eligible for reimbursement at all and patients have to pay for these out of pocket making the case for the use of generics and biosimilars even more compelling. Cost is one of the most significant contributory factors leading to premature cessation or interruption of therapy.
- (ii) The availability and assurance of supply of branded products are erratic. Having a pool of generic suppliers and products ensures the availability of products and reduces the risks associated with reliance on one innovator product, which may not be available regularly in-country in several low-income countries. There have been cases of stock outs of oncology medications leading to frustrations among patients coupled with loss of confidence in the health care system and compromised care in general.
- (iii) There are limited suppliers of innovator oncology medicines due to the huge cost associated with the acquisition and supply. Also, the absence of suitably qualified personnel means that most pharmacies do not routinely stock oncology medicines unless specifically requested for by prescribers. In addition, dispensers (pharmacies) often insist on getting some assurance of regular requests for products in order to stock them. Absence of firm and regular orders means that procurement of these products will be done on *ad hoc* basis. However, the lower cost of generics and the need for generic manufacturers to penetrate the market create other suppliers with more flexible terms of procurement and supply.
- (iv) There are few or no local manufacturers of innovator oncology medicines in low-income countries. However, local manufacturers are able to produce generic versions of long-standing products like methotrexate. In India, manufacturers are able to produce biosimilar versions of monoclonal antibodies and other biological products used in oncology.
- (v) The campaign to promote prescribing of medicines by their generic (international non-proprietary names) means that local and national treatment guidelines and essential medicines list only specify medicines by their generic names. This allows dispensers to dispense the available version of the requested medicine regardless of who the supplier is. This saves patients from the frustration of looking for branded products which may not be readily available.

Table 1. Cost of generic and branded cancer medicines in Ghana

Name of medication	Cost price GHC (generic)	Cost price GHC branded
Adriamycin 50 mg	6.00	<i>Myocet</i> 1367.04
Anastrozole (28) 1 mg	198.00	<i>Arimidex</i> 207.40
Bicalutamide Tabs (28) 150 mg	50.40	<i>Casodex</i> 720.00
Bortezomib Inj 3.5 mg	Not available	<i>Velcade</i> 3850.002
Docetaxel Inj 20 mg	95.20	<i>Taxotere</i> 320.00
Docetaxel Inj 80 mg	261.00	<i>Taxotere</i> 1263.00
Tamoxifen 20 mg	28.5	<i>Nolvadex</i> 30.00
Vincristine Inj 1 mg	8.00	<i>Oncovin</i> 42.54
Vinorelbine Inj 50 mg/5 ml	205.00	<i>Navelbine</i> 419.94
Zoledronic Acid Inj 4 mg	165.00	<i>Zometa</i> 549.90
Trastuzumab 120's	–	<i>Herceptin</i> 8300.00
Bevacizumab 100 mg	–	<i>Avastin</i> 1820.00

1USD—1.92 GHC.

potential problems with generics

- (i) Quality assurance and quality control including the fact that in case of unexpected failure of therapy, it is difficult to assign a cause for the failure. Is it due to the product, the regimen or the dosage? Or is it due to the stage of the disease and other patient factors? Since multiple factors determine outcomes in oncology, the case for generics should be strongly made that no generic should ever be of inferior pharmaceutical integrity to the innovator branded product. Where treatment outcomes are unfavourable, it is important for prescribers to be able to rule out convincingly any contribution from the generic or biosimilar product used. Where doubt exists as to the integrity of the product or the circulation of counterfeit or substandard products in the supply chain, prescribers may opt only for innovator or branded products despite the high cost and erratic availability of these.
- (ii) Supply chain integrity. Oncology products are very expensive and therefore attractive to dealers in spurious, sub-standard, fake, falsified and counterfeit medical products. Since generics are multisource, it is difficult to guarantee the integrity of the supply chain since the players are numerous and varied. It is estimated that there are more than 1000 manufacturers of generic oncology medicines in India alone with similar (albeit lower) numbers in China. Generics coming from certain markets, e.g. ICH countries often come with the assurance of a developed country regulator's inspection but those from less developed but active pharmaceutical markets may not be so well regulated.
- (iii) Safety and safety monitoring of medicines for oncology is poorly done in all settings. While innovator products are often required to have stringent post-authorisation safety monitoring systems, the same cannot be said of generic and biosimilar oncology medications. Since safety of products depends not just on the active ingredient but also on the manufacturing process, excipients, storage etc, it is important that generic and biosimilar products are monitored actively for their safety and effectiveness. The performance of these products when stored in the high temperatures of tropical countries is also an important factor and one that requires monitoring especially in the case of biosimilars which may require maintenance of a stringent cold chain.
- (iv) There are currently no WHO-prequalified products for oncology and medicines for cancer care. Since there are no large donors and global agencies purchasing oncology medicines, their procurement is left to national agencies or individual hospitals and pharmacies. There is therefore no reason for manufacturers to seek WHO pre-qualification. Countries, to procure quality assured products, therefore have to rely on their own regulatory system or else purchase more expensive generics and biosimilars from

ICH countries rather than rely on products from South East Asia whose quality they may not be able to assess.

discussion

It is evident that much needs to be done to improve the spectrum of cancer control in Africa and other low income regions. Generic drugs and biosimilars, appropriately priced and quality controlled have an obvious role to play in the management of established cancer and their availability must be promulgated, with a particular focus on potentially curable cancers. One other area of linked activity could be in the development of treatment guidelines for low-income countries. Currently, the majority of cancer treatment guidelines produced by the major professional societies recommend therapy with very expensive branded medicines which are stratospherically out of the reach of cancer patients in low-income countries. We believe that it would be timely to establish therapeutic guidelines developed by and aimed at cancer health professionals and their patients, to provide cost-effective solutions for cancer care in low-income countries. The World Health Organisation may also have to considering generic medicines and biosimilars in its medicines pre-qualification scheme.

disclosure

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