Financial Toxicity of Cancer Drugs: Possible Remedies from an Ethical Perspective

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Summary

Spiraling costs of cancer treatments have become a major concern for the payers in the health care system and for individual patients suffering from the cancer drugs' financial toxicity. This article discusses possible solutions from an ethical perspective. First, it gives some orientation about what constitutes a fair price for innovative anticancer agents. While a definitive answer remains difficult, there are good reasons to enter into price negotiations with the pharmaceutical companies to align the price with the R&D costs and the added value of the product. Information about the drug's cost-effectiveness should be available, a fixed threshold, however, seems ethically problematic. Rather, a 'signal cost-effectiveness threshold' should indicate when the drug price requires special justification. Further strategies include an improved benefit assessment after market authorization by independent publicly financed studies, which will provide a valid basis for price negotiations and clinical decision-making at the micro level. Last but not least, cancer treatments should be tailored not only to the biology of the tumor but also to the preferences of the patient. Primarily mandated by the respect for autonomy, promoting patient-centered care has the potential to improve quality of care and enable a wise use of scarce health care resources.

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Introduction

Advances in molecular biology, especially in molecular genetics, have spurred innovation in cancer therapies. Under the terms of 'personalized medicine' or 'precision medicine', novel treatment strategies have been developed with the promise to increase not only the effectiveness but also the efficiency of patient care by tailoring the intervention to the individual patient. While the term 'personalized medicine' raises the expectation that the novel treatments are tailored to the person in a comprehensive sense, most innovations occur at the biological level. Based on a systematic review of 2,457 articles containing the term 'personalized medicine' (PM) in the title or abstract, we derived the following definition of PM: 'PM seeks to improve stratification and timing of health care by utilizing biological information and biomarkers at the level of molecular disease pathways, genetics, proteomics as well as metabolomics.' [1]. A paradigmatic example for such biomarker-based stratifying treatment strategies is the use of trastuzumab for metastatic breast cancer in patients overexpressing the HER2 receptor. Many of these new therapies, however, provide a comparatively small additional benefit for the patients, e.g. prolongation of survival time by several weeks to a few months, while treatment costs often exceed €100,000 per year [2, 3]. Spurred by the expectation of high profit margins, the pharmaceutical companies have many new anti-tumor agents in the pipeline which will come onto the market during the next years. In an aging society, there is an increasing incidence of cancer with a growing demand for cancer treatment. At the same time, most health care systems around the world have come under increasing financial pressure, hence raising concerns about how the spiraling costs of cancer drugs can be covered in the upcoming years, with the risk of limited public coverage of cancer drugs and resulting inequities in access to effective cancer care. At the individual level, there are increasing concerns that patients will come under extreme financial pressure if they have to bear the 'financial toxicity' [4] of cancer treatments due to insufficient or lacking insurance. This ar-

ticle discusses the ethical implications of the increasing prices and budget impact of cancer drugs: Are the high prices of cancer drugs justified? How can public health care systems react appropriately to the increasing financial pressure due to the escalating costs of cancer drugs? First of all, however, it has to be clarified if and in which way the escalating costs for cancer drugs are of ethical relevance.

High Costs of Cancer Drugs – an Ethical Issue?

Many goods and services have become more expensive over the last years without raising ethical concerns. Health care, however, is a special good as it contributes to improving individuals' health which is a prerequisite for realizing any life plans one could have. Thereby, health care contributes to a fair equality of opportunity which is a requirement of liberal justice [5, 6]. Therefore, there are good ethical justice-based reasons for equal access to at least a basic benefit package of health care services, e.g. provided by a publicly financed health care system with universal coverage. Costs of health care matter as there is a limited budget for public spending, and increases in health care expenditures are associated with opportunity costs in other publicly financed domains like social security, education, or infrastructure (while investments in these areas often have positive effects on people's health status!). Limiting the overall amount of public health expenditures therefore seems ethically justified. However, it is difficult to determine what the 'right' level of health care expenditure shall be. As a consequence, escalating health care costs put public health care systems under increasing financial pressure as the overall health care budget cannot and should not be expanded indefinitely.

As the cost pressure cannot be compensated by increases in efficiency (at least not in the short run and not completely), most health care systems are left with no other option than to limit the services covered by the public system – which is commonly referred to as rationing [7]. As a result, patients have to pay for services out of pocket [4] or, where there is not enough money, go without the needed health care which is problematic from a fairness perspective. If drug prices keep increasing and consume an ever-growing portion of the health care budget, this will inevitably result in health-related inequities. Therefore, the escalating costs of cancer drugs do constitute an ethical issue, and we have to find ways of dealing with the price increases in an ethically justified manner. One of the most straightforward options would be to reduce the prices of anticancer drugs. In the next section, we will therefore discuss whether the high cancer drug prices are or can be justified.

What Is a Fair Drug Price?

Prices for cancer drugs have increased considerably over the last years, more than most other goods and services. The price range of anticancer drugs has more than doubled over the last decade, from \$4,500 to more than \$10,000 per month [2]; in the US, the direct

costs of cancer care are projected to rise from \$104 billion in 2006 to over \$173 billion in 2020 [8]. According to Fojo and Grady [9], an 18-week treatment with cetuximab for non-small cell lung cancer (NSCLC) increases the overall survival by 1.2 months at an average cost of \$80,000. Extending the life of 1 cancer patient by 1 year would cost about \$800,000. And cetuximab is not an exception, most anticancer agents approved by the FDA cost more than \$20,000 for a 12-week course of treatment. These figures show why the high costs of cancer treatments are so concerning: It is not just the price itself, but the relationship between an incredibly high price and a comparably low benefit for the patient, often accompanied by severe side effects. Is this a wise use of limited health care resources which most likely could achieve a bigger overall health gain if spent somewhere else to prevent or treat diseases?

Whether or not these high prices for anticancer drugs are justified is not easy to determine. In an unregulated competitive market, prices are determined by the interplay of supply and demand, and reflect, at least to some degree, the added value of the product to the consumer. During the time of patent protection, however, pharmaceutical companies are granted an artificial monopoly with the possibility to set the price at their own discretion, irrespective of the added benefit to the patient. This allows the company to recoup the high expenditures for research and development (R&D) that went into the drug development, which are usually much higher than the production costs. The pharmaceutical industry often justifies the high prices with the rising drug development costs which are to some extent beyond the control of the pharmaceutical companies [2]. Regulatory requirements, for example, have increased over the years and contribute to the higher R&D costs. Other cost factors, however, can be attributed to the pharmaceutical industry, like costs for lawyers and contract research organizations (CROs) or so-called pay-for-delay deals in which pharmaceutical companies with patent-protected drugs pay other companies to delay the introduction of generic versions [2].

Determining exactly what constitutes a 'fair' price for a new drug remains difficult. Possible justifications could follow 2 different lines of argument. The first argument can be derived from the justification of the patent-protected monopoly: A price is justified only insofar as it allows the pharmaceutical company to recoup its R&D investments, including the costs for drug development failures [10], plus a reasonable profit. However, pharmaceutical companies are currently not required to disclose their true R&D costs, which therefore cannot be taken into account in the drug pricing negotiations. And even with a requirement for disclosure, pharmaceutical companies most likely would try to boost the development costs which in turn would require further burdensome controls. The example of imatinib, one of the most successful targeted cancer therapies, reveals that pharmaceutical companies try to maximize their profits far beyond recouping their R&D costs [11]. While imatinib was initially priced at \$30,000 per year in 2001, a reasonable price which allowed the drug manufacturer to recoup R&D costs within 2 years, the price increased to \$92,000 in 2012, despite the fact that the market for imatinib had widened due to approval of the drug for new indications. These prices can no

longer be justified by the underlying rationale of the patent system and should not be accepted by public and private payers.

According to the second possible line of argument, the price of a drug should reflect its true benefit and societal and personal cost [2]. In principle, this is a straightforward argument: A better drug justifies a higher price. However, the devil is in the detail. First of all, a valid assessment of the drug's added net value (benefit 'minus' burdens and harm) is required, which is often not available when it comes onto the market (see below). Second, if we have a valid net-benefit assessment, we must determine what price is appropriate in relation to a certain incremental benefit. To pick up the example of cetuximab again: Is \$80,000 for a prolonged overall survival of 1.2 months an appropriate price (or \$800,000 for 1 added year of life, respectively)? In the following section, we will discuss in more detail how the question of an appropriate cost-effectiveness or cost-benefit threshold should be handled. A third challenge is that therapeutic progress is often incremental, especially in the development of effective cancer drugs. New anticancer agents are often first tested in those patients in whom all other available treatments have failed, i.e. cases which are especially difficult to treat. The first studies may therefore underestimate the agent's true added value and the resulting price may be too low, which would be a disincentive for the pharmaceutical industry to invest in further drug discoveries. This does not mean that negotiations about drug prices should not reflect the added value of the product. It rather points to the potential challenges that should be taken into account, especially the question of what constitutes an appropriate price for a certain incremental net health benefit – which we will discuss in the following section.

Cost-Effectiveness Threshold as a Solution?

One possible solution, which is often discussed among health economists and practiced by the UK's National Health Service (NHS), is to perform cost-effectiveness analyses and set a threshold for a maximum ratio between costs and effects (or benefits) that is acceptable for coverage. Economic evaluations often use the QALY (quality-adjusted life year) as a generic measure for health benefits (cost-utility analyses), where the health gain of 1 QALY constitutes 1 additional year of life with full quality of life. This generic measure of medical benefit, which integrates the 2 dimensions of life expectancy and quality of life, allows a comparative assessment of cost-effectiveness across different diseases and service areas. In the health economics literature, a cost of \$50,000 per QALY is often discussed as the threshold for cost-effective care. The UK National Institute for Health and Care Excellence (NICE) considers interventions as cost-effective if the costs to the NHS are less than £20,000 per QALY gained. Interventions costing between £20,000 and £30,000 per QALY may also be considered cost-effective under certain conditions. According to its policy, however, NICE does not reject interventions based on cost-effectiveness alone, i.e. the threshold is not categorical.

Especially under the constraints of limited resources, assessing the cost-effectiveness of health interventions is not only attractive

from a health economics perspective but it is also justified from an ethical point of view. It makes the opportunity costs of health investments transparent and thereby contributes to making the best use of scarce health care resources in terms of health gain per money spent, which is mandated by the ethical principle of utility maximization. Furthermore, this can contribute to a fair allocation of resources because resources spent on services with bad cost-effectiveness can be reallocated to other health care areas which are underfinanced. However, pure utility maximization in the health care system would not be ethically acceptable. As we have learned from the first priority list of the Oregon Health Plan, an allocation based on the criteria of cost-effectiveness alone leads to a counter-intuitive and ethically unacceptable ranking of services, because it neglects the severity of disease and the size of the incremental individual benefit to the patient [12].

Likewise, a fixed cost-effectiveness threshold would be ethically unacceptable because it would exclude patients from health care who require resource-intense treatments to achieve a comparatively small health benefit. As argued elsewhere, it would be acceptable to have a 'signal cost-effectiveness threshold' above which a special justification is required to accept a higher price per QALY gained [13]. Possible justifications include high severity of disease, a big incremental health benefit for the patient, or great innovative potential of the intervention (i.e. potential benefit for future patients). In addition, a cost-effectiveness threshold could lead pharmaceutical companies to lower their prices, which does not only happen in the UK's NHS but also in other Western health care markets [2]. Fairness requires, however, that cost-effectiveness considerations are made at the system level (all patients are treated by the same rules and standards) and are not applied to single patients. An acceptable application could be cost-conscious guidelines which limit expensive treatments within a particular indication (disease) to those patient subgroups who benefit most from it [14, 15]. Patient subgroups who would derive just a small incremental benefit from the expensive treatment would have to go with a cheaper therapeutic alternative.

Another important concern is the validity of the cost-effectiveness assessment in cancer care: Often there is just limited evidence about the effectiveness or the benefit of new anticancer agents after market authorization. Therefore, any economic evaluation of cost-effectiveness also has limited validity and is not a sound basis for making coverage decisions with significant implications for the patients. Consequently, we should first improve the effectiveness or benefit assessment under routine conditions after market authorization before basing coverage decisions on a cost-effectiveness threshold, which will be discussed in the following section.

Perspective 1: Improving the Benefit Assessment of Anticancer Drugs

If new anticancer agents come onto the market, not only their efficacy and safety (which have been studied prior to market authorization) should be known but also their incremental benefit,

i.e. the added value for the patients under routine clinical conditions. This information is important at both the system and the individual level: At the system level, it can provide important input into price negotiations between public payers and pharmaceutical companies. According to the German Act on the Reform of the Market for Medicinal Products (AMNOG), for example, newly authorized drugs are subject to an early benefit assessment by the Institute for Quality and Efficiency in Health Care (IQWiG), which compares the added medical benefit of the new agent to the appropriate standard therapy. The results are then used in the negotiations between the Federal Joint Commission (G-BA) and the drug manufacturer about the price which the statutory sickness funds will pay for the new drug (www.english.g-ba.de/benefitassessment/information/). If there is no evidence for an additional benefit, the drug is included in the reference group of comparable drugs with a fixed price.

At the individual level, valid knowledge about the added value of the new anticancer agent is important for clinical decision-making, both for physicians and patients.

At the time of market authorization, however, there is only limited knowledge about the added benefit of the new drug under routine conditions for several reasons. The studies required for drug licensing usually assess the efficacy under ideal conditions based on selected non-representative samples. Often, surrogate endpoints are used like progression-free survival or time to tumor progression, instead of patient-relevant endpoints like overall survival or quality of life. In many cases, a head-to-head comparison with standard treatment is missing, which makes it difficult to assess the incremental benefit, i.e. the added value of the new anticancer agent. Finally, there often is incomplete data transparency due to selective reporting and publication bias. Taken these factors together, the requirements for a valid benefit assessment are often not met at the time of market authorization which has negative implications at both the system and the individual level: At the system level, a valid basis for price negotiations reflecting the added value of the new product is missing, while at the individual level, physicians and patients lack relevant information for clinical decision-making.

The first priority should therefore be to improve the benefit assessment after market authorization under routine clinical conditions by independent clinical studies which can address open patient-relevant issues [16]. Increased public funding should be available for these studies. One option could be that during this initial phase, the new drug is only covered within clinical studies ('coverage with evidence development'). These independent studies will not only allow a more rational and efficient allocation of scarce health care resources but also improve the quality of care for cancer patients. Based on this more valid information about the net benefit under routine conditions, economic evaluations can assess the cost-effectiveness of the new anticancer agents, which can then serve as a valid basis for price negotiations with the pharmaceutical companies. Coverage of interventions with a small incremental benefit and a bad cost-effectiveness ratio could be limited (i.e., exclusion of 'pseudo-innovations'), while real innovations with a significant added value would be available to all patients without restrictions.

Perspective 2: Improving Patient-Centered Care

Given the high costs of cancer treatments, it is even more important to make sure that the cancer treatment is tailored not only to the biology of the tumor but also to the individual preferences of the patient. Studies indicate that severely ill patients' preferences are often not adequately respected if they prefer palliative treatment over aggressive life-prolonging care. In a study by Teno et al. [17], 86% of the patients who wanted aggressive treatment reported that their care was consistent with their preferences, while only 41% of those who preferred palliative care reported that their care was consistent with their wishes, resulting in considerably higher estimated mean 1-year costs of care. Apparently, patients' preferences for comfort care are often not elicited and/or respected, which does not only violate the ethical obligation of respect for autonomy but also constitutes a misuse of scarce health care resources, which is ethically inappropriate from the perspective of distributive justice.

The seminal study by Temel et al. [18] points to a similar direction. Patients with metastatic NSCLC were randomly assigned to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone. The patients who received early palliative care did not only report improved quality of life and mood but also had less aggressive care near the end of life and a longer median survival. Apparently, early palliative care was able to reduce unnecessary and burdensome anticancer treatment for the benefit of both the patient and the health care system. Studies from other medical areas support the observation that improving patient-centered care in patients with severe life-threatening diseases has the potential of reducing overuse of health care resources. Effective involvement of cancer patients, however, requires a specific attitude and communicative skills in the sense of shared decision-making, truly enabling these patients to make their own individual choices. Advance care planning (ACP), for example, a systemic intervention to improve patient-centered decision-making for future crises in which patients have lost their decision-making capacity, has proven to be effective in safeguarding patient autonomy [19], and has the potential to reduce the cost of care near the end of life [20]. A large trial evaluating the effect (and cost-effectiveness) of ACP in patients with progressive cancer is currently underway [21]. Given the high cost of life-prolonging therapies not only in oncology, tailoring the use of these treatments to the individual preferences of the patient is certainly an ethical obligation of the highest priority.

Conclusion

The spiraling costs of anticancer drugs do not only put public and private payers in the health care system under increasing financial pressure but often also pose a financial threat to cancer patients. As a consequence, the extremely high prices may limit the access to effective cancer treatments and thereby raise ethical issues of distributive justice. While it is difficult to determine what is a

fair price for an innovative anticancer agent, the current pricing practice of the pharmaceutical industry can often not be justified, neither by the need to recoup high drug R&D costs nor by the therapeutic benefit for the patient. Price negotiations with the pharmaceutical industry are therefore ethically mandated, if possible based on a valid assessment of benefits and costs. This is currently a major challenge, as the therapeutic benefit under routine conditions cannot be assessed based on the licensing studies. Therefore, independent publicly funded clinical studies after market authorization are required to answer the open patient-relevant questions and provide a valid assessment of the drug's added value. This information can then be used at the system level for price negotiations and at the individual level for the process of informed (shared) decision-making between physicians and patients. While information about a drug's cost-effectiveness should be available in

negotiations to make opportunity costs transparent, a strict cost-effectiveness threshold would not be ethically acceptable. Rather, a 'signal cost-effectiveness threshold' could be defined, demanding special justification if the price of a drug leads to a cost-effectiveness ratio above the threshold. Last but not least, the use of innovative anticancer drugs should not only be tailored to the tumor's biology but also to the individual preferences of the patient. Doing less against the tumor can mean doing more for the individual patient.

Disclosure Statement

The authors declare that they have no competing interests.

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