COMMERCIAL DETERMINANTS OF CANCER MEDICINES

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Summary: Europe is experiencing a 'value crisis' for cancer medicines. Whilst some therapeutic innovations have delivered substantial clinically meaningful benefits, many new cancer drugs benefits are marginal. At the same time prices (and overall costs) have dramatically increased. The reasons behind this are multifactorial. Multi-level intervention including changing the narrative of patient organisations, altering the clinical communities acceptance of poor quality clinical trials, integrating socio-economic studies, requiring a balanced portfolio approach from public funders, raising the regulatory requisites and embedding health technology assessment will all be needed to ensure valuable, sustainable and equitable cancer medicines.

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Introduction

In the last decade, cancer drugs have become the main focus of research, clinical care and health budget spending across Europe.[1] The molecularisation of cancer in terms of understanding it through molecular-level factors such as genes and hormone receptors rather than environmental or behavioural factors, has led not just to its pharmaceuticalisation [2] but also to medicines gaining a dominant position in the social psyche of cancer care.[3] Oncology as a domain has reversed decades of productivity decline in the biopharmaceutical industry, leading to extraordinary returns on investment. But this has come at a cost. Whilst a range of new cancer medicines, notably in the immuno-oncology class, have added substantial clinically meaningful benefit, many have not. Moreover, even among those medicines which do appreciably improve outcomes, their prices (and overall therapeutic costs – diagnostics, toxicity management, etc.) are posing inherent risks to a system which unduly rewards low value cancer drugs.[4,5]

Here we explore the concepts of value in cancer care, current spending on cancer medicines, lessons from trials and routine clinical practice. These concepts can provide insight into whether private sector commercial interests can co-align with public sector interests or whether their diverging trajectories pose a significant threat to Europe's future ability to deliver equitable and affordable cancer care.

The Problem with Value

The oncology community currently faces a crisis in the way the value of cancer medicines is interpreted. Clinicians conceptualise value as the relationship between magnitude of benefit (net of side effects) and costs.[6] The numerator (i.e. magnitude of benefit) represents the interface between the measure which

is improved (i.e. overall survival (OS), quality of life (QOL), or alternative endpoints) and the magnitude of improvement (i.e. effect size). Given that the goal of any medical intervention is to help patients live longer and better lives, the primary endpoint of all oncology trials should be OS and/or QOL. Yet, the oncology community has widely embraced the concept of "surrogate" endpoints; predominantly progression-free survival (PFS).[7]

> "rushing to embrace early access schemes despite their well known drawbacks

PFS is a composite endpoint representing time to tumour growth on imaging and/or death. It was initially designed as an intermediary endpoint to guide decision-making for early phase trialists in identifying which compounds to move from phase I/II to phase III testing. It was not originally intended to be an endpoint that should influence clinical care. However, over the past two decades, it has become the most common primary endpoint in oncology randomised controlled trial (RCTs) as its use dramatically shortens duration of clinical trials and recruitment numbers.[8]

While there are a handful of circumstances in which PFS is known to be a valid surrogate for OS, this represents a small minority of contexts in which it is used.[9] Most contemporary oncology RCTs either do not measure OS or find no benefit in OS. Accordingly, we find ourselves in a scenario in which most new cancer medicines are known to shrink tumours on imaging but likely do not help patients live longer lives. It has also been shown that PFS is not an appropriate surrogate for QOL.[10] Even among those new cancer medicines which do improve OS, the average gains in survival are very modest.

Box 1: The UK Cancer Fund

A special body called "The NHS Cancer Drugs Fund" (CDF) was established in the UK in April 2011, as result of patient association advocacy, to improve access to cancer drugs. The CDF had a budget to provide funding for orphan indications or rare conditions that NICE would ordinarily not appraise.[16]

The CDF had an initial budget of €50 million per annum with the plan to move towards a value-based pricing scheme by 2014. The fund benefitted over 95,000 patients, with its budget reaching €200 million in 2011/2012 and €340 million in 2015/2016 following public pressure demanding access to new cancer medicines.[16]

Economists established that the fund diverts NHS money to cancer, irrespective of the low survival rate of some drugs.[17] A study published in 2017 revealed that the CDF had not delivered meaningful value to patients. Since its creation, out of 47 CDF approved indications, only 18 (38%) showed a statistically significant OS benefit, with an overall median survival of 3.1 months. With very minimal or no benefit in survival, most of the drugs did not reach the threshold of meaningful clinical benefit and indeed NICE had previously rejected 26 (55%) of the CDF approved indications because they did not meet cost-effectiveness thresholds.[15]

As the fund failed to provide meaningful value to patients, it was merged with NICE.[16] This example shows that reacting to lobbying efforts without informed analysis of the drugs can create negative consequences. Better-informed pressure from patients and professionals would have saved a large amount of money which could have been allocated to supportive care for cancer patients (psycho-social support) or to other diseases.

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Price of Cancer Medicines

While the numerator (i.e. effect size) of new medicines is small, the denominator (i.e. price) is staggering. The prices of cancer medicines impact at two levels. First, in health systems without universal coverage they can lead to serious out-of-pocket expenditure (financial toxicity) that generates dramatic inequalities. In addition, at the societal level, the impact on health and cancer budgets leads to opportunity costs which can 'crowd out' funding for other areas of cancer care. Even if a cancer medicine is cost-effective, it may be unaffordable.[11] The commercial model that delivers low-value, high-priced cancer medicines also incentivises poor drug development. Thus the commercial aspects of cancer medicines are, from an economic perspective, intimately linked to all the technologies we use in cancer care. The average annual price for a new cancer medicine is rising rapidly and now approaches $150,000.[12] It is now well established that private sector investment in research and development cannot explain these prices. Making the high prices even more problematic is the observation that there is no relationship between the magnitude of benefit and price within the cancer medicine ecosystem and where prices increase over time despite a supposedly 'competitive' environment.[13] The current approach to cancer drug pricing appears to be driven not by any rational economic policy, but by the upper bounds of what the market will bear, even in times of financial crisis.[14]

Regulatory and Political Challenges

In most countries and regions of the world, including in Europe, governance mechanisms to increase the value of cancer medicines are insufficient. Health technology agencies have struggled to maintain a high enough bar in the face of

political pressure. And where they have achieved this, e.g. the United Kingdom's National Institute for Health and Care Excellence (NICE), political expediency, and lobbying using the narrative around ensuring better and quicker access to medicines has created bypass mechanisms such as the Cancer Drugs Fund in the UK that has led to massive financial losses (**see Box 1**).[15] The lessons from the first iteration of the Cancer Drugs Fund have not been translated internationally; with new plans to facilitate early access to drugs that have not even received regulatory approval but are considered "promising," many European Union countries are rushing to embrace early access schemes despite their well known drawbacks.

Such ease of market access and rapid clinical development and entry into markets has meant that among the world's ten largest pharmaceutical companies, revenues generated by sales of cancer medicines increased 70% between 2010 ($56 billion) and 2019 ($95 billion) while revenues from other medicines decreased by 18% (from $342 to $282 billion). The European biopharmaceutical sector, supported by federal and philanthropic funders who have significantly aligned their budgets to focus on basic cancer sciences and cancer medicines, has dominated the European Research Area since its inception. From a societal perspective, it is worth considering that population-level European cancer health outcomes are unlikely to improve given the focus on the metastatic disease, with many new cancer medicines delivering less than 2–3% of survival benefit. Many policy discussions have lost the wider perspective, including QOL, socio-economic impacts, and other key dimensions.

A Research Ecosystem that is Not Delivering Value

Observations from the cancer research ecosystem offer critical insights into the current low-value cancer medicines crisis. Our group has tracked temporal trends in industry-sponsored oncology RCT design and results since 1975. Among trials of cancer medicines in breast, non-small cell lung, and colorectal cancer foundational changes, include:

1) a shift away from government funding towards industry (which now funds ~90% of all cancer drug RCTs);
2) a massive increase in sample size (with the resulting statistical power to detect a very small difference between treatment groups);
3) a shift away from overall survival as the primary endpoint (PFS is now the endpoint in ~40% of RCTs compared to ~30% for OS); and
4) among those trials which do show improved OS, the gains are modest with average improvements in median survival of two to three months.

Data from the global landscape of cancer RCTs show that 87% of all cancer RCTs test medicines rather than new surgical or radiotherapy techniques. For Europe, this means that patients are not receiving treatments and systemic therapies that we know work, i.e. there are implementation and access barriers to evidence-based care. This needs parallel investment in understanding the drivers and necessary improvements on a health system level.

> "policy discussions have lost the wider perspective, including quality of life and socio-economic impacts

Real-world data is not a Panacea

Is public sector real-world data (RWD) a panacea for making up for the failure to design and deliver marketing authorisation trials that produce data that can determine whether a medicine delivers clinically meaningful benefit? While there are many important uses of RWD (i.e. to understand access, quality, outcomes), the growing movement towards using RWD for regulatory decision-making and even as a replacement for the RCT is very concerning and may lead to the adoption of cancer medicines with little benefit and perhaps even net harm.[18] Our group recently reviewed all RWD studies (n=293) for cancer drugs approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) during 2010–2015.[19] Some 78% of these studies were of low methodologic quality. Most studies (63%) reported inferior survival in routine practice compared to the relevant RCTs; RWD studies that reported superior outcomes to RCTs (which should be viewed with great scepticism based on everything we know about the efficacy-effectiveness gap) were most likely among low-quality studies of RWD.

Solutions

The private sector now determines nearly the entire biopharmaceutical (cancer medicines) ecosystem across Europe, for which it enjoys massive public sector research funding alignment. Whilst this certainly provides certain European countries (including the UK) with competitive, wealth-generating cancer research economies, as well as some truly novel cancer medicines that deliver clinically meaningful benefit, our assessment is that, overall, the commercial determinants of cancer medicines in both research and care are creating an unsustainable situation both in terms of delivering better outcomes and more affordable, equitable cancer care systems. So, what are the solutions?

First, Member States must introduce high standards, both at the national level and through stronger health technology assessment mechanisms, coupled with more sophisticated pricing and reimbursement systems. But at the heart of this is a cultural change required in clinical/medical oncology that no longer accepts poor quality clinical trials, that does not engage in the hype surrounding some new medicines and pursues fair prices as a central tenant of clinical

care. A new contract with private sector interests for cancer medicines must also include the major federal and philanthropic research funders and better national policy around the choice architecture of payment systems. Our data show that their respective research portfolios are massively un-balanced.[20] More funding needs to be re-allocated to the public sector, investigator-driven medicines research and trials, health services and systems research as well as a major drive to integrate socio-economic studies into clinical trials of medicines. These multi-level actions are essential if valuable commercially-driven cancer medicines research is to deliver better, more equitable and affordable care across Europe.

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Screening: When is it appropriate and how can we get it right?

By: A Sagan, D McDaid, S Rajan, J Farrington, M McKee

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Technological and other scientific advances have made it possible to screen for ever larger numbers of molecules and see inside the human body with a level of detail that was once unimaginable. Where there is good evidence that detecting a condition early will, overall, be beneficial for those who are screened, then it may be appropriate to design and implement a formal screening programme.

However, just because something can be done does not mean that it should be done as screening may bring benefits as well as harm. In this brief the authors start by explaining the core components of a screening programme, highlighting that, while seemingly simple, putting together all elements of a screening programme is very complex.

They then ask when screening should be done, emphasizing the continued relevance of Wilson & Jungner's screening principles. In addition, they examine the pressures to implement screening and, where screening is inappropriate, suggest ways to reduce it. When screening is appropriate, evidence is presented on how to achieve optimal results. This brief is an essential reading for anybody involved in the decisions on screening or its provision.