European Journal of Cancer (2013) 49, 2777–2783

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Position Paper

How can innovative forms of clinical research contribute to deliver affordable cancer care in an evolving health care environment?

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Available online 15 June 2013

KEYWORDS
Pay for performance
Observational cohort studies
Real life data
Clinical trials
Public private partnership

Abstract As health care costs are constantly rising and governments are reforming their healthcare systems there is an urgent need to reshape the European clinical research landscape. To bridge the translational gap extensive research to understand the mechanism of the agents and of the disease has to be performed and the real benefit of drugs needs to be assessed independently. Furthermore, meaningful data for reimbursement strategies will be a major goal of future clinical trials as well.

Therefore, a new integrated model of clinical cancer research is needed to optimise the R&D process. Strategies to ensure that we can gather robust and relevant data about the effectiveness of various healthcare interventions have to be developed to provide optimal patient care within the limits of a healthcare budget.

1. Introduction

Propelled by an increasing understanding of the mechanisms and pathways of tumour biology, clinical cancer research has truly entered a promising era filled with exciting new possibilities. Innovative options for prevention, diagnosis and treatment of cancer patients are under development, and these, combined with advances in technology, means there is still a lot more to come. However, the current clinical trial landscape cannot fully embrace these advances. In order to harness these possibilities and turn dreams into reality, stakeholders need to work together within an integrated cancer clinical research environment that is able to address the questions that are relevant today.

Genomic sequencing will become more and more common as costs continue to decrease tremendously. In 2001, sequencing a human-sized genome cost nearly $100,000, but this price dropped to under $8000 in 2012. Looking forward, advances in sequencing technologies together with progress in bioinformatics for creating, storing and analysing data will lead to even more opportunities. On the other hand, this could create unforeseen obstacles, as the sheer volume of newly

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http://dx.doi.org/10.1016/j.ejca.2013.05.016

acquired data will need to be analysed, understood and interpreted.

'Translational science' has been a catch phrase for over a decade, but until now, no major breakthroughs in research and development (R&D) have been achieved.[1] In fact, the stark reality about developing new drugs is disappointing: the number of drugs approved by the FDA (United States Food and Drug Administration) and the EMA (European Medicines Agency) has remained in the 20–25 range during the past few years. The recent productivity of the pharmaceutical industry has been low. Roughly 5.000–10.000 compounds need to be developed and screened to realise a single approved drug. Of the initial number of candidate compounds, 250 are closely investigated in the preclinical phase, and only five ever reach the clinical phase, but reaching the clinical phase is no guarantee of success. More than 51% of new drugs fail in clinical Phase II trials due to a lack of efficacy, and even more, 66%, fail in Phase III.[2]

The numbers are similar for new molecular targeted agents (NMA), and during the past decade, there has been a marked decline in productivity. From 2003 to 2007, 34% of NMAs progressed from Phase II to Phase III compared to just 22% during the 2007–2011 period.[3]

The entire drug development cycle, from discovery to final approval, takes about 10–15 years on average, and here, too, the trend is disappointing for NMAs. The duration of this development cycle for NMAs rose from 11.4 years in 1999–2001 to 13.7 years in 2009–2011. In oncology, which when compared to other specialties within the field of clinical medicine has the highest failure-rate for late stage clinical trials the overall success rate from first-in-man to registration is about only 5%.[4,5]

The average cost to develop and market a new drug, including the cost for failures, has increased by more than 60% from 2000 to 2005.[6] The complexity of clinical trials and regulatory requirements has been increasing over the last years. The consequence of this is, of course, that the pharmaceutical industry must invest considerable time, effort and financial resources to have any hope of obtaining one profitable drug. Only about two of every 10 marketed drugs generate sufficient revenues to cover their associated R&D cost.[7] Adding to the worries of the pharmaceutical industry, competition is getting tougher. On average, a new drug faces generic competition after 11.8 years, but generic companies can challenge as soon as 4 years after a new drug has entered the market.[8] And some countries are trying to develop more relaxed patenting standards in order to facilitate access for low-income countries to new drugs as recently demonstrated in India for sorafenib tosylate.[9]

Another challenge is 'me-too' drugs. Market competition among drugs targeting the same pathway may reduce the costs for all drugs of this therapeutic class and lead to optimised drugs. But the concentration of resources on conditions for which treatment options do already exist is not in the best interest of society.[10]

In developed countries the ageing population is growing rapidly, and these socio-demographic changes, together with increasing costs due to new technologies and drugs, will inevitably increase the costs for healthcare systems. Healthcare, and in particular cancer care, is already expensive. In Europe, the total expenditure on healthcare is about 10% of the national gross domestic product (GDP), and it is even higher in the United States of America (USA) at about 14%. These costs are rising at a rate higher than that of inflation. In 2000 the expenditure on health in Europe was 8.0% of GDP and increased to 9.3% in 2009, while in the USA over the same time period the health care expenditure increased from 11.4% to 14.4% of GDP.[11] Hence governments are reforming their healthcare systems to cut the costs.[12]

In the future, healthcare providers will need to be increasingly restrictive about the reimbursement of new expensive drugs, and they will certainly demand solid data with a clear proof of benefit before paying.

In Europe, several countries have already developed their own strategies concerning the process for deciding reimbursement based on the specific national settings. Since different countries have different guidelines for what is reimbursable, this could lead to a diverse healthcare landscape across Europe. There are already differences in cancer survival within Europe: survival rates in northern Europe (especially Sweden) are higher than in eastern Europe (Czech Republic and Poland).[13] These differences may increase in the future, because the discrepancies in the standard of care might become greater between the different countries depending on the implemented reimbursement strategies.

Altogether, it is strikingly obvious that healthcare systems face daunting challenges, and collaboration of all stakeholders – pharmaceutical industry, academia, regulatory authorities and last but not least patient advocacy groups – is needed to develop strategies that can provide optimal patient care within the limits of a healthcare budget. Therefore, a new integrated model of clinical cancer research is needed to optimise the R&D process and develop and implement strategies to ensure that we can gather robust and relevant data about the effectiveness of various healthcare interventions.

2. Clinical trial environment today and future developments

Personalised medicine requires the development of targeted agents either alone but most often in combination (sometimes with approved drugs and/or other therapeutic strategies such as radiotherapy). This is