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Current Perspective

‘Mind the gap’ between the development of therapeutic innovations and the clinical practice in oncology: A proposal of the European Organisation for Research and Treatment of Cancer (EORTC) to optimise cancer clinical research

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Abstract In Europe, most of the cancer clinical research dedicated to therapeutic innovations aims primarily at regulatory approval. Once an anticancer drug enters the common market, each member state determines its real-world use based on its own criteria: pricing, reimbursement and clinical indications. Such an innovation-centred clinical research landscape might neglect patient-relevant issues in real-world setting, such as comparative effectiveness of distinct treatment options or long-term safety monitoring.

The European Organisation for Research and Treatment of Cancer (EORTC) advocates reforming the current ‘innovation-centred’ system to a truly ‘patient-centred’ paradigm with systematically coordinated applied clinical research in conjunction with drug development, featuring the following strategy:

(1) An interconnected partnership among key-stakeholders involved in the care delivery system, namely patients, health professionals, academia, pharmaceutical industry, regulators, payers and policy-makers, to optimise the transition from research to clinical practice and vice versa;
(2) An independent research infrastructure host and coordination ensuring independent, high quality and sustainable research.

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1. The limits of an 'innovation-centred' system for the development of anticancer treatments in Europe

1.1. Regulatory approval does not guarantee patients' access to innovative treatments

Twenty years ago, the former *'European Agency for the Evaluation of Medicinal Products'* started to standardise the registration of new drugs on the continental scale. Registration by the agency (now referred to as *'European Medicines Agency'* (EMA)) was likely to have provided patients with innovative treatments, responsible for 40% of the improvement in patient overall survival (OS) from 1982 to 2001 [1]. Since then, the markets and the prices of anticancer drugs have increased drastically, however, with less substantial clinical benefit [2]. Despite a centralised registration, the reimbursement of new drugs occurs at a national level, enabling the European member states to conduct independent public health policies. Moreover, as the rate of further reimbursement keeps decreasing, the unequal access to anticancer innovations would continue to worsen the existing differences in OS across Europe [3,4].

Countering the constraining public health policies enables cancer patients to benefit from new treatments. Lobbying by patients, clinicians and charities may put pressure on health technology assessment (HTA) agencies. In 2009, in the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE), earlier known as the National Institute for Clinical Excellence, backed off and finally validated the reimbursement of sunitib for patients with metastatic kidney cancer in the UK [5]. Off-label and 'compassionate' use of new drugs may improve the access of cancer patients to these innovations. Yet, these temporary and non-standard clinical practices could lead to more aggressive and non-evidence-based care, decrease patients' accrual into clinical trials (CTs), thereby impairing possibilities for research [6]. When an as-yet approved drug has not been reimbursed, investigators are likely to launch new CTs using this treatment to facilitate its use [NCT03013335]. Conducting CTs in low-income countries may improve local patient access to innovations in the short-term, but often with suboptimal comparator making interpretation on the efficacy of the anticancer treatment difficult [7].

1.2. Real-world issues on treatment indications are not sufficiently addressed

The regulatory approval of new treatments does not address clinical issues relevant to patients in real-world settings, such as:

(1) How is the new treatment compared to the optimal therapeutic option according to routine clinical practice?
(2) What are the clinical outcomes when the new treatment is administered in real-life cancer patients or in off-label indications?
(3) Would it be better if the focus is shifted as to how to combine and/or sequence the new treatment with the existing therapeutic options?
(4) What is the optimal administration scheme/treatment duration and at which benefit/risk ratio?
(5) What are the patients' preferences regarding multiple therapeutic options?
(6) What are the long-term issues related to the treatment?

When addressed, the aforementioned questions are studied mostly after EMA's approval and rely on the goodwill and agendas of independent research groups [8].

There are many reasons for such lack of real-world evidence. First, regulatory approval of new treatments requires data on 'quality, safety and efficacy' and not 'comparability'[9]. This approach is centred on the innovative treatment as its value is assessed in absolute terms, not relatively to the pre-existing therapeutic armamentarium. Second, the end-points used to register a treatment might lack clinical relevance [10]. For example, in prostate cancer, a study showed a discrepancy between, on the one hand, physicians and patients' clinical priorities such as quality of life (QoL) and on the other hand, questions addressed by clinical relevance [11]. Third, patients included in cancer CTs represent only 2–4% of the overall targeted population to maximise the experimental treatment effect, leading to a poor external validity of CTs [12]. Finally, evidence lacks to rank multiple therapeutic options available and to define the conditions for optimal cancer care [13]. There is a clear research gap between drug development and real-world health care delivery which has been illustrated in Fig. 1.

2. The need for new partnerships among stakeholders involved in the health care delivery system

2.1. Disconnected stakeholders leading to a fragmented process

Although targeting the same goal – the so-called 'improvement of patients' care', the stakeholders who are part of the development of anticancer treatments have distinct priorities. While pharmaceutical companies seek – among others – profit, researchers want to develop their medical armamentarium and academic career, regulators assess the absolute therapeutic efficacy, and payers make sure that the medical innovations are worth the public investment. Each stakeholder defines the value of a new treatment from distinct angles (Table 1). This fragmented process results in two disconnected stages from drug development to real-world application. In the first stage, scientific issues on