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Review

From bench to clinical trials the EORTC experience in biology-based clinical cancer research

Konstantinos Tryfonidis *, Katherine Hartmann, Marie Morfouace, Denis Lacombe

European Organization for Research and Treatment of Cancer (EORTC), Av. Mounier 83/11, 1200 Brussels, Belgium

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ABSTRACT

For over 50 years the European Organization for Research and Treatment of Cancer (EORTC) has delivered major advances in cancer clinical research and cancer therapeutics. The introduction of molecularly targeted agents has led to significant improvements in outcome for patients with specific tumor types; however conventional chemotherapy remains the mainstay of treatment for the majority of patients. Due to increasing knowledge about the diversity of molecular pathways driving malignant progression, strategies to integrate biology into clinical research and development are continuously evolving. The challenges and the experience of the EORTC regarding how translational research is to be an indispensable component of the clinical research environment, which aims to deliver more sophisticated treatment approaches will be discussed in this perspective article.

Contents

Introduction

Traditionally treatment of patients with cancer is based on certain clinical-pathological characteristics consisting of the organ in which the tumor originated as well as the extent of the disease, as captured by the size of the primary tumor, the nodal involvement and the presence or absence of distant metastases, as reported by the TNM (tumor, node, and metastasis) classification. In some tumor types, certain biomarkers, expressed by the cancer cells such as the estrogen receptor (ER), the progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status in breast cancer play an increasingly important role in therapeutic decision-making [1]. In recent years, further basic research in the field of cancer genomics has revolutionized cancer management by interpreting and assigning clinical significance to genomic alterations, e.g. Epidermal Growth Factor Receptor (EGFR) gene activating mutations are associated with response to tyrosine kinase inhibitors (gefitinib and erlotinib) for patients with non-small cell lung cancer (NSCLC) [2,3]. As the number of these potentially relevant genomic alterations is increasing, it becomes necessary for

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* Corresponding author at: EORTC Headquarters, Av, Mounier, 83/11, 1200 Brussels, Belgium.
E-mail address: konstantinos.tryfonidis@eortc.be (K. Tryfonidis).

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them to be tested in a clinical research framework, where not only their prognostic but also their predictive value can be addressed. In this perspective article, we present the experience of the European Organization for Research and Treatment of Cancer (EORTC), a unique, pan-European academic clinical research organization with global reach for developing and conducting such biologically-driven clinical trials and we elaborate on the challenges and the impact that such studies may have.

Cancer morphology or cancer biology?

Histological evaluation of cancer by pathologists has revealed several subtypes which have been used for years to tailor treatment approaches. However, cancers are highly complex and are often driven by genetic aberrations that result in signaling pathways controlling proliferation and growth becoming constitutively active [4]. Recent advances in molecular biology technologies such as gene expression profiling analysis and next generation sequencing have resulted in a better understanding of the pathways, as well as their respective molecular components aberrations contributing to cancer development. Interrogating such genomic aberrations to identify those that influence genome stability, chromatin structure, differentiation, RNA processing and beyond, may improve our understanding of the molecular landscapes of cancer. Combining pathological and genomic data can provide a better understanding of the tumor and clinical response and help develop novel therapeutic strategies [5]. New WHO classifications for specific tumor types have already begun combining genomic alterations with "classical" pathology assessment to better stratify patients (e.g. medulloblastoma classification in the 2016 WHO classification, 4th revisited edition) [6]. However, genomic alterations identified in one tumor type cannot be broadly applied to others, due to extensive intertumor heterogeneity across different tumor entities; importantly, the same molecular aberration can have different relevance across different tumor types; for example, in patients with untreated metastatic melanoma with *BRAF* V600E mutation, Vemurafenib, a specific BRAF inhibitor showed an increase in 6-month overall survival (OS) compared to dacarbazine (84% vs 64%) [7]. On the contrary, the same inhibitor in colorectal cancer patients with the *BRAF* V600E mutation showed no clinical efficacy [8]. Functional molecular studies provided the mechanistic explanation for this discrepancy, emphasizing the need to couple clinical development of new targeted agents with rigorous basic and translational research [9,10]. The development of new drugs and new therapeutic strategies on the basis of the disease biology will constitute a critical step in implementing personalized medicine in cancer. It will ultimately involve connecting cancer genome events with their clinical significance in an evidence-based manner.

The evolution of cancer therapy

The clinical management of cancer patients has traditionally relied on chemotherapeutic choices that are selected based on the underlying histology and are directed against all cells, cancerous or not, on the basis of rapid cellular division rates. In the recent years, improved understanding of the molecular biology of cancer coupled with advances in the medicinal chemistry shifted the focus to the clinical development of molecularly targeted agents. Despite the initial hope that such agents would target and therapeutically block some of the cancers 'Achilles heels', clinical reality indicates that even in success stories, resistance can occur, due to the plasticity of cancer cells and their ability to adapt to the selective pressures exerted by targeted agents [11,12]. Therapeutic resistance to targeted agents can be mediated by both pathway-dependent and -independent mechanisms [13]. Pathway dependent mechanisms include additional genetic alterations within the target oncogene itself, activation of a critical parallel mechanism that is not influenced by the targeted therapy, genomic alterations that deregulate signaling proteins acting either upstream or downstream of the target oncoprotein; while pathway independent resistance mechanisms include the tumor microenvironment and altered tumor angiogenesis. Pathway-dependent and pathway-independent mechanisms of drug resistance could of course develop simultaneously and this complicates more the development of effective clinical therapies to overcome resistant mechanisms of cancers [14]. Although we have already proceeded a step further by therapeutically harnessing the immune system against cancer, an approach, which is conceptually different from what has been described above, the integration of cancer biology in therapeutics remains critical in identifying the patient population, which can derive the utmost benefit from a specific treatment (Fig. 1). To take into consideration tumor heterogeneity, or overcome resistance to targeted therapies, combination studies are being developed. In the case of immune-therapies, understanding the role of the micro-environment in tumor development is important. For example, pre-clinical models of pancreatic tumors are showing that a so-called "cold" tumor can become infiltrated with activated tumor infiltrating lymphocytes (TILs) and respond better to standard therapy (e.g. Gemcitabine) when a combination of anti-PD-L1 and FAK inhibitors (targeting the Cancer-Associated Fibroblasts) is given [14]. Combining therapies that target different parts of the "Hallmark of Cancer" could help overcome low clinical efficacy or resistance to single agent therapies [4].

The EORTC biology based clinical trials

During the last decades, EORTC has embraced the latest developments of cancer research, successfully developing biology-based

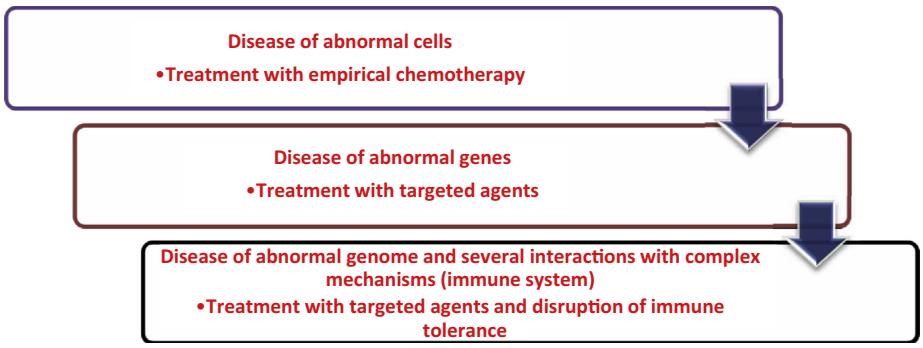

Fig. 1. Evolution of cancer treatment.

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