Cancerworld

Tackling resistance to anti-EGFR therapies, from challenges to re-challenge

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Since their first approval and use, more than 15 years ago, inhibitors of the Epidermal Growth Factor Receptor (EGFRi) have revolutionized the clinical practice and the prognosis for cancer patients, especially those diagnosed with colorectal (CRC) and lung cancer. These drugs rapidly shifted the treatment paradigm of the two malignancies from traditional chemotherapy to targeted therapy and are now considered the standard-of-care for metastatic CRC (mCRC) with wild type RAS and no mutations in EGFR (in combination with chemotherapy) and non-small cell lung cancers (NSCLCs) harbouring specific EGFR activating mutations (Troiani T, et al. ESMO Open 2016; Karachaliou N, et al. Trans Cancer Res 2019).

“EGFR-tyrosine kinase inhibitors are miracle drugs: patients with lung cancer simply go back to life after being treated,” said Yosef Yarden, Professor in the Department of Biological Regulation at the Weizmann Institute of Science, Rehovot (Israel). “But this is just a temporary miracle” he added,

highlighting one of the major challenges anti-EGFR therapy comes with: resistance, that usually occurs about one year after starting the treatment (Sullivan I, Planchard D. Front Med (Lausanne) 2017; Zhang Y-C, et al. Cancer Letters 2019; Takeda M, Nakagawa K. J. Mol. Sci. 2019). "No doubt that resistance is the biggest clinical issue we must deal with before and while treating patients with these drugs" stated Fortunato Ciardiello, Professor of Medical Oncology and Dean of the School of Medicine and Surgery, Università degli studi della Campania Luigi Vanvitelli, Naples (Italy).

What are we talking about?

In 1986, the Nobel Prize in Physiology or Medicine was awarded to Italian biologist Rita Levi-Montalcini and the American biochemist Stanley Cohen "for their discoveries of growth factors", the latter mainly focusing on epidermal growth factor (EGF) (The Nobel Prize in Physiology or Medicine 1986. NobelPrize.org). With a history started in the mid-'50s of the last century, EGF and its receptor (EGFR) suddenly started playing a pivotal role in basic and clinical research, leading researchers to gain a deep knowledge of physiological and pathological roles of these molecules, as well as their structural and molecular characteristics. The transmembrane protein EGFR is involved in tumour growth, survival and immune-escape and it is now considered one of the most potent genes commonly altered in cancers.

Moving from the bench to the bedside, targeting EGFR tyrosine kinase activity headed to the development of many cancer therapeutics (Thomas R, Weihua Z. Front Onc. 2019; Troiani T, et al. ESMO Open 2016; Karachaliou N, et al. Trans Cancer Res 2019). Two classes of drugs have been specifically developed targeting EGFR and are currently approved – as previously mentioned – for use in the setting of metastatic CRC and NSCLC, respectively: monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). As first postulated by John Mendelsohn and Gordon Sato in 1980, mAbs against EGFR (namely cetuximab and panitumumab) prevent ligand binding to the receptor, thus inhibiting the activation of the specific tyrosine kinase cascade of events and, consequently, blocking cancer cell proliferation.

As far as it concerns TKIs, small molecules competing with ATP in binding to the intracellular TK domain of EGFR (Troiani T, et al. ESMO Open 2016), three generations of drugs are now available. First-generation TKIs (erlotinib, gefitinib) are active in patients with diseases harbouring sensitizing mutations in EGFR TK domain, while second-generation drugs (afatinib, dacomitinib) were developed to overcome resistance to first-generation TKIs due to the acquisition of T790M mutation in the TK domain of EGFR. The simultaneous inhibition of the mutated and wild-type form of the receptor leads to dose-limiting toxicities for the second generation of TKIs and determined the development of a third-generation of TKIs (osimertinib), with increased specificity for T790M mutation and a low inhibitory effect on wild-type EGFR (Westover D, et al. Annals Oncol 2018; Sullivan I, Planchard D. Front Med (Lausanne) 2017; Zhang Y-C, et al. Cancer Letters 2019).

Resistant (or sensitive) to the bone

Several clinical studies demonstrated that EGFR targeted therapies are highly effective in sensitive cancers, improving progression-free survival (PFS), objective response rates (ORRs) and quality of life while decreasing toxicity compared to previous standards-of-care (Yamaoka T, et al. Int J Mol Sci. 2017; Karachaliou N, et al. Trans Cancer Res 2019). But a glitch is just behind the corner, being that sensitive cancers actually represent a limited fraction of all CRC and NSCLC. "In both colorectal and lung neoplasms, the indication for anti-EGFR drugs includes only selected population of patients" Ciardiello explained, stressing the concept of innate resistance and activating (also called "sensitizing") mutations that must be taken into account when choosing the best therapeutic approach. Starting from CRC, the expert reminded that anti-EGFR mAbs can only be used in patients with wild-type RAS (both KRAS and NRAS) cancers, accounting for about 40% of all mCRCs, and

that mABs are more effective in left-side primary tumours. Shifting the attention to NSCLC, it's clear that the percentage of patients who can benefit from EGFR TKIs is even lower. The presence of sensitising mutations in the EGFR TK domain of the receptor is, in fact, necessary for these drugs to be effective. The most common, accounting for 90% EGFR mutation in the clinic, are deletions in exon 19 and L858R mutation in exon 21 (Yamaoka T, et al. Int J Mol Sci. 2017; Westover D, et al. Annals Oncol 2018). "In the so-called Western countries sensitising mutations are detected in 12-15% of the cases, while in Eastern Asia they are more common, usually in a 30-35% range, reaching 50% in specific populations" said professor Yarden. "Moreover, we know that EGFR sensitising mutations are mostly found in non-smokers, are more common in women – most of them in their childbearing age – than in men. Why this happens is not yet clear" he added.

Dynamic landscapes

Almost all patients treated with an anti-EGFR drug, both mABs or TKIs, develops resistance even after an impressive initial response. In recent years, many mechanisms of acquired resistance to EGFR inhibitors have been elucidated, showing a very dynamic molecular and cellular landscape and a great number of different processes involved. To make a long story short, is it possible to cluster resistance mechanisms at least in three major groups: gene mutations, activation of alternative pathways and phenotypic transformation (Yamaoka T, et al. Int J Mol Sci. 2017; Parseghian CM, et al. Clin Cancer Res. 2019). For example, the emergence of the missense T790M mutation within exon 20 of EGFR is the predominant mechanism of resistance to first- and second-generation TKIs, occurring in 50-70% of patients progressing after treatment (Sullivan I, Planchard D. Front Med (Lausanne) 2017; Zhang Y-C, et al. Cancer Letters 2019). "Unfortunately, resistance also occurs after the use of third-generation TKIs like osimertinib due to several mechanisms like the emergence of a tertiary mutation, namely C797S" claimed Yarden. Activation of alternative pathways, including upregulation of other members of EGFR family (HER2 or HER3) or mutation in BRAF can also be involved in acquired resistance, as well as the transformation from NSCLC to SCLC (small cell lung cancer) or epithelial-mesenchimal transition of cancer cells (Yamaoka T, et al. Int J Mol Sci. 2017; Westover D, et al. Annals Oncol 2018; Parseghian CM, et al. Clin Cancer Res. 2019). "This is a very complex scenario, but the good news is that many of the players involved in acquired resistance can be studied as potential targets for new therapies to prevent, delay or overcome resistance" Ciardiello added.

Stepping out the box

Progress has been made in identifying cellular and molecular mechanisms responsible for resistance to anti-EGFR drugs. Nonetheless, the question remains on how to counteract this phenomenon. When resistance occurs, patients are often treated with chemotherapy, alone or in combination with other drugs (e.g., anti-angiogenic drugs). It could definitely work in some cases even if, as recently reported in a paper published in Cancer Letters, "novel agents with higher potency, broader selectivity and better intracranial activity are urgently needed" (Zhang Y-C, et al. Cancer Letters 2019). New drugs are in fact under development still targeting the EGFR TK activity but, getting a glimpse to the known resistance mechanisms, it appears that TK activity is only the beginning of the story and it could be worth looking a little bit further. "We could think, for example, to use different approaches targeting both the kinase activity of EGFR and alternative pathways" said Yarden. In his laboratory, experiments are ongoing in mice carrying human tumours (xenografts) using a double anti-EGFR strategy (mAb + TKI) together with a blockage of human epidermal growth factor receptor 2 (HER2), somehow activated after EGFR inhibition. "This combination showed a very strong synergistic effect and all the tumours disappeared during the treatment. As observed with other therapies, also this triple regimen failed to cure patients: the tumour always comes back if we stop administering the drugs" Yarden explained. Good results have been observed also in mCRC,

where new regimens combining inhibition of wild-type EGFR and mutant BRAF are combined" added Ciardiello. Finally, it is important to note that the optimization of the sequence of administration of anti-EGFR drugs, especially TKIs, has not been determined and it is highly warranted (Takeda M, Nakagawa K. J. Mol. Sci. 2019).

New technologies and tools on board

In such a complex molecular scenario, effective tools are needed to analyse and monitor changes that can inform therapeutic choices. As reported in an editorial published in Annals of Oncology, "Molecular profiling of NSCLC is now critical not only at the time of diagnosis, but even so at each step of tumour progression due to molecular alterations in the tumour" (Vansteenkiste J, Wauters E. Annals Oncol 2018). The same is true for mCRC, where molecular characterization is mandatory before starting the treatment with anti-EGFR mAbs and is of pivotal importance when considering a second- or third-line therapy (Parseghian CM, et al. Clin Cancer Res. 2019). A tissue biopsy can be used to identify the presence of the molecular requirements for a specific anti-EGFR treatment, like sensitising mutations in NSCLC, but cannot be repeated too often in the clinical setting. "We need a non-invasive procedure that can be performed quite often without bothering or damaging the patient" said Ciardiello. "Liquid biopsy and the analysis of circulating tumour DNA (ctDNA) acquired from a simple blood draw could be the answer: it gives us a real-time molecular picture of the tumour and it is as specific and sensitive as tissue biopsy" he added, highlighting that ctDNA analysis could be a successful approach to overcome the issue of intra-tumoural heterogeneity. "The ctDNA represents a 'summary' of cancer DNA: the analysis of these small fragments allows us to gain information about the whole tumour in one run" the expert claimed. Last but not least, high-throughput techniques like new generation sequencing (NGS) should be mentioned. "I think that every patient should go for NGS to detect mutations in his/her disease. This will help define a personalized treatment and collect molecular data to better understand and maybe overcome resistance mechanisms" claimed Yarden.