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Anti-Tumour Treatment

Personalized treatments of cancer patients: A reality in daily practice, a costly dream or a shared vision of the future from the oncology community?

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ABSTRACT

Therapies targeting activated oncogenes have been associated with several successes in the last decades that are described in this review, together with their limits and related unsolved questions. Most of the tumours will eventually develop drug resistance potentially due to intratumor heterogeneity and selection of additional molecular events. Moreover, studies in the field of molecular characterisation of cancers have shown that most tumors include large number of rare genomic events. Developing new drugs requires the use of large-scale molecular screening programs to enrich phase I/II trials with patients presenting the genetic alterations to treat them with the appropriate drug(s). Administering one single drug will incur in non-durable results, so the future is to cleverly combine drugs. Development of personalized immunotherapeutics and/or anti-angiogenic agents could change the natural history of several cancers. Finally, other systems including DNA repair and metabolism have become targetable.

These considerations justify the development of molecular medicine with the characterisation of each tumour to assess defects in all the systems previously mentioned to propose a unique combination of therapies to each patient. Current drug development is clearly not appropriate, and studies with drugs given in relevant combinations should be favoured by new relationships between academia and industry. New organisational and medico-economics approaches are required to minimize the financial burden of personalized medicine by considering the foreseen decrease of the costs of new technologies, and the money saved by avoiding the use of many costly, useless but nonetheless toxic treatments given after failure of standard therapy.

Introduction

Advances in biology and technologies have dramatically changed the way cancer patients are being treated. First, high throughput sequencing of the major cancers has provided a better understanding of molecular mechanisms that generate malignant transformation and cancer progression. The so-called oncogenic drivers will allow initial steps of the oncogenesis. Oncogenic drivers are usually generated by genomic alterations, like ERBB2 amplification, EGFR mutations, B-Raf mutations etc... Targeting these oncogenic drivers is called "oncogene de-addiction" and is expected to result in tumor shrinkage. Secondary events will be involved in cancer resistance and metastatic dissemination. As an illustration, *EGFR* T790M and *ESR1* mutations mediate resistance to EGFR inhibitors and endocrine therapy, respectively. A major challenge in molecular medicine will be to target these secondary events early enough, in order to avoid treatment resistance. Whether these genomic alterations are present as a "minority subclone" in the initial tumor or are acquired during cancer progression is still an open question. Furthermore distinct phenotypic and mutational profiles that can occur within different localisations in the same tumor (intratumor heterogeneity) and genomic instability (the elevated rate of spontaneous molecular alterations occurring in tumors) are involved in the Darwinian selection of minority clones and potentially responsible for the development

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of resistance to oncogene de-addiction. Although kinase activation has dominated the field of personalized medicine in the last decades, several new areas of cancer biology including DNA repair and metabolism, are having an increasing impact in the field. Finally, recent data suggest that targeting immune suppression networks could be a major way to control cancer progression, and that mechanisms of immune suppression are individual.

The second revolution in cancer research was the use of high throughput technologies for treatment decision. Early studies have shown that next generation sequencing and gene expression arrays can be performed on the vast majority of patient samples, with a robust assessment of the genomic profile.

Overall the unique and 'personal' history of each cancer has now been clearly revealed by technological developments that are now been evaluated as tools to guide treatment decision in personalized medicine initiatives. In the present manuscript, we will review which of these technologies are the main pillars of personalized medicine for cancer treatment, and we will discuss the potential developments to be expected. The scope of this review will not include patient's stratification for prognosis, or prediction of toxicities but will instead focus on promising genomic tests that show potential to improve outcome in the metastatic setting.

Targeting the drivers: is the bottle half full or half empty?

c-Kit

Imatinib (Gleevec®, Novartis) is a tyrosine-kinase inhibitor (TKI) that represents the paradigm of a successful targeted agent, due to its highly efficiency towards its expected target c-abl and the oncogenic fusion product bcr-abl systematically present in chronic granulocytic leukemias (CGL) [1]. The introduction of Imatinib in medical practice has radically modified the therapeutic options available for the two human malignancies, CGL and gastrointestinal stromal tumors (GIST), which commonly bear activating mutations of either c-kit or PDGF-RA [1,2]. Interestingly, the drug not only gives an initial response, but also leads to long term stabilization. Imatinib consequently became the illustration of the "oncogenic drivers" concept postulating that that cancer control can be achieved by targeting these oncogenes. It later became clear that imatinib not only targets c-kit in GIST, but can also activate innate immune response, that could contribute to its efficacy.

Her2

Her2 is encoded by the gene *ERBB2* that is amplified in around 10% of breast cancers. Trastuzumab (Herceptin®, Roche) is a humanized monoclonal antibody that targets extracellularly Her2 by acting on its domain IV [3]. On the other hand, Lapatinib is a tyrosine kinase inhibitor that targets both Her2 and EGFR. Overall, both agents provide very limited efficacy as single agents. This is the case as well for the recently approved monoclonal antibody Pertuzumab (Perjeta®, Roche), that targets as well extracellularly HER, but in it case by blocking the domain II (the ligand domain) [4]. Response rate associated to the administration of pertuzumab as monotherapy and after failure to trastuzumab are around 3%.

These data emphasize the limits of oncogene de-addiction as "isolated" strategy. The results obtained with these drugs became clinically relevant when they started to be used in combination with chemotherapy.

Trastuzumab has widely proved its efficacy in metastatic disease, in various combinations with other conventional drugs notably chemotherapy but also endocrine therapy [5–8]. Furthermore, two large European and American studies have clearly demonstrated the benefit of adding trastuzumab to conventional chemotherapy in the adjuvant setting for HER-2 positive patients, with both studies showing significant benefits in both disease-free and overall survival (OS) [9,10]. The use of tyrosine kinase inhibitors allows the antitumor effect of targeting the Her2 driver to be more accurately assessed. Lapatinib (Tykerb® GSK) is a small molecule inhibitor having affinity to the intracellular domains of both HER-2 and EGFR1 [11]. Similarly to trastuzumab, lapatinib has been shown to improve outcome of patients with Her2-overexpressing breast cancers. Interestingly, when the drug is delivered to adequate dosages, the TKI was as effective as the monoclonal antibody in terms of pathologic complete response [12,13], but was less effective in the metastatic setting [14]. As for trastuzumab, the drug provides relevant antitumor effects only when combined to chemotherapy.

As for imatinib, trastuzumab was initially presented as a success story of oncogene de-addiction since it could lead to long-term progression free survival (PFS). Nevertheless, the global picture of Her2 targeting by trastuzumab is by far more complex. Indeed, there is now large body of evidence that immune system contributes to the efficacy of trastuzumab [15] and could have an impact on the long-term outcome.

Moreover, higher benefit has been observed with the concomitant administration of two anti-Her2 therapies (trastuzumab + lapatinib or pertuzumab) in combination with chemotherapy, both in the metastatic and the neoadjuvant settings when compared to a single anti-HER2 therapy [13,16–19]. Moreover, significant activity has been seen in a small subgroup of patients with just two targeted therapies (even in the absence of chemotherapy) [17]. In fact, approval for Pertuzumab was obtained in association with trastuzumab and the chemotherapy docetaxel for patients with metastatic HER2-positive breast cancer previously untreated [19].

Overall, the key messages from the Her2 story are: (i) activating immune system in parallel to oncogene de-addiction could improve outcome (ii) oncogene de-addiction synergizes with chemotherapy and, (iii) blocking the same receptor by two different agents derives in higher benefit. Even though the mechanisms of this synergism are unknown they could involve immunogenic cell death.

ALK and EGFR in NSCLC

Genomic studies have over years demonstrated the large interpatient heterogeneity of non-small cell lung cancer (NSCLC). Clearly far from being only one item [20,21] NSCLC is now subdivided in many entities based on the presence of oncogenic drivers. The two most illustrative drivers in lung cancers are *EGFR* mutations and *EML4-ALK* translocations [22].

In the first Phase I–II trial testing the anti-ALK inhibitor Crizotinib (Xalkori®, Pfizer), a total of just only 82 patients with NSCLC harbouring *EML4-ALK* translocation were included. The results appeared quite spectacular with 57% of partial responses [23]. Based on results of this phase II trial, the drug was approved in US. The EMA forced Pfizer to conduct a randomized phase III trial comparing in second line ALK + NSCLC patients standard chemotherapy to crizotinib [24]. The ethical implications of this trial were partially mitigated by the possibility given for a cross-over upon progression of those ALK-translocated patients that were randomized to the chemotherapy arm.

Overall, the illustration of *EML4-ALK* is highlighting the question about what level of evidence is needed before registering a targeted therapy. In the context of NSCLC where OS is limited, some regulatory agencies have approved crizotinib without a randomized trial. The scenario would have been different in other tumor types where OS can reach four years in the metastatic setting.