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Current challenges and future perspectives in the medical treatment of solid tumours

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ABSTRACT

We are making progresses in the treatment of cancer. Vaccines are effective in preventing hepatocellular carcinoma, cervical and head and neck carcinomas. The use of adjuvant or neoadjuvant medical treatments in breast, colon, rectal, ovarian and gastric cancer produces additional cure rates of 10–30%. And chemotherapy, hormonal treatment, and biologic agents have improved the outcome of metastatic cancer in every solid tumour, including the most refractory. However, resistance continues to be the main reason for failures in the advanced setting, and this is more pronounced amongst certain tumours where the progresses have been much limited: melanoma, biliary tract cancer, oesophageal, non-small cell lung cancer, brain tumours, etc. There are four main challenges for the near future: a better classification of tumours; a simplification and acceleration of the drug development process; a more courageous drug design and drug approval process.

1. Introduction

We are making progresses in the treatment of both early and advanced solid tumours. These progresses involve every aspect of oncology, both clinical and experimental. In general, we may say that progresses are more evident on the preclinical, experimental side. Thus is certainly true: suffice it to think of the human genome sequencing, and to the shift from the biochemical approach to the molecular approach to study the transformed phenotype that has occurred since the early 1980s. However, one must consider the simplicity of the experimental tumour systems, relative to the extreme complexity to common human solid tumours. Thus, it is easy to understand that the results in the field of clinical human cancer management must be less spectacular.

This concept granted, one cannot fail to recognise the relevant clinical advancements of the last 10–15 years. Vaccines are available and demonstrate efficacy in the prevention of hepatocellular carcinoma, cervical and head and neck carcinomas.[1,2] The use of adjuvant or neoadjuvant medical treatments in breast, colon, rectal, ovarian and gastric cancer produces additional cure rates of 10–30% (on top of those afforded by surgery alone). And chemotherapy, hormonal treatment and biologic agents have improved the outcome of metastatic cancer in every solid tumor, including the most refractory (renal cell, GIST, hepatocellular carcinomas),[3–5] so that the classical distinction operated 10–15 years ago of advanced cancers into 'resistant, sensitive and curable' tumours has been revolutionised. In fact we now know that medical treatment of metastatic colorectal, gastric and pancreatic cancers, once classified as highly resistant, quadruplicates the median survival compared to the best supportive care. This is not the same as saying that we are doing so well in pancreatic or gastric cancers: their median survival continues to be too short (7–10 months), but clinically important responses to treatment can be obtained in 20–40% of patients with these prohibitive common solid tumours.

Resistance to medical treatments continues to be the main reason for failures in the advanced setting, and this is more pronounced amongst certain tumours where the progresses have

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been much more limited: melanoma, biliary tract cancer, oesophageal, non-small cell lung cancer, brain tumours, cervical, endometrial cancers and soft tissue sarcomas and the above-mentioned colorectal, breast, gastric and pancreatic cancers.

There are three main challenges for the near future: a better classification of tumours, no longer based upon the morphology, but on their molecular characteristics; a simplification and acceleration of the drug development process; a more courageous drug design and a drug approval process that is more focused on the clinical relevance of the data rather than on their statistical significance.

2. The need for a better classification of tumours

Shortly after the discovery of the microscope in the 19th century, cancer has been recognised as a cellular disorder. Then the distinction amongst epithelial, mesenchymal and lymphoid origin has been made, to generate the more recent classification of neoplasms based upon their organ and tissue of origin. It is a common experience, though, that morphologically identical cancers may have dramatically different clinical courses. Hence the need to recognise factors that may improve the prognostic accuracy. The tumour grading system helps somehow under this respect, and the several morphologic characteristics that the pathologists report further refine this attempt; however, the problem remains. After the explosion of the notions about the molecular mechanisms responsible for the uncontrolled cell proliferation, the capacity to evade apoptosis, the tendency to invade adjacent tissue, trigger angiogenesis and disseminate (the key features of the malignant phenotype, Hanahan 2000 Cell)[6] it seems reasonable to think that tumours could be classified according to these features and this classification should allow a better prognostic rating of the individual patient's tumours.

An additional advantage would be the fact that the key determinants of this classification would be at the same time the target of novel biologic agents and thus this prognostic classification should also be predictive of drug effect. This is the hope for the future. But it is something that must happen and will indeed happen for sure: we already have the new biologic agents targeting the molecular determinants of the key features of the transformed phenotype ... and we can call these '21st century agents'. It makes little sense to use these against neoplasms classified according to a 19th century system.

There are already very good examples of this correspondence operating in the clinic. Hormonal receptors and HER-2 for breast cancer; K-ras for colorectal cancer; c-KIT for GIST; activating mutations of EGFR for non-small cell lung cancer. It is extremely likely that this list will grow exponentially so that we will witness an overlap between the old morphologic classification and some of these new molecular parameters that will be more and more frequent to the point of substituting the old system.

3. Simplification and acceleration of the drug development system

Targeted agents are successful in common solid tumours. With rare exceptions, when successful, they are actually more successful than cytotoxic chemotherapy. In fact PFS increments of >50% in breast, colorectal, renal and hepatocellular carcinoma have been obtained in randomised trials, compared to largely inferior increments in successful chemotherapy trials.

More than 500 antineoplastic agents are in the clinical phase of development: more than the sum of the next two most represented therapeutic classes, antiinfective and digestive system drugs (Chabner JCO 03).[7] The constant advances of our understanding of uncontrolled cell proliferation and the other key features of the transformed phenotype will make this number to grow further in the next future. The cost of approved biologics is already very high, too high for their indiscriminate use in all patients with the same histopathologic tumour type This is due to the high development cost, approximating 1 billion dollars: 2/3 of this is spent for the preclinical phase (accounting for all the agents failing before reaching the clinical stage); 1/3 is spent for the clinical phase, 75% of which for phase III development.

All these figures point out to the need of accelerating the entire process of drug development, so that we will be able to recognise promising agents earlier, exclude inactive agents and pursue clinical development shooting for registration of a small, selected number of compounds with a high chance of success.

Today this remains a hope because there are two main obstacles to simplification and acceleration.

The first regards the little predictive power that preclinical screening systems have in identifying agents that will work in the clinical setting. This is generally true at the level of both new compound design and their screening against experimental tumour systems. The common thought of experts, when asked an opinion on whether to go for clinical development or not to go, is that it is always very good to have a rationale and good supportive preclinical data, but that is not enough. Thus that decision continues to be terribly difficult.

The second obstacle regards the time and cost of the clinical development phase, especially the registration phase, usually dependent upon lengthy and costly phase III trials. As it will be illustrated in the next two sections, there are suggestions that may shorten the time and reduce the cost of drug development, but the problem is the price to pay, i.e. the chance to miss some potentially effective agents, as we will see.

4. The need for a more courageous design of trials in advanced solid tumours

Once the preclinical and clinical data regarding a novel agent are encouraging enough the decision to go for a randomised phase III is taken. Then the issue becomes what the target delta of the trial is going to be. This is a crucial step, because if the delta is very low (say 10%) the chances of success are going to be high, but the number of patients needed to demonstrate this small difference is very high as well, making the cost and the time terribly high and long. In addition, even if the trial is successful, the relevance of a 10% improvement may be marginal (we are dealing with incurable conditions anyway).

Two key questions drive the choice of the target delta in comparative clinical trials: 'what is the plausible delta' and 'would that delta be worthwhile for the patients'. So far, priority has been given to the first question rather than to the second; this is due to two reasons:

- The recognition that 'superstars' in the treatment of common solid tumours are the exception and that the progresses in oncology are incremental.
- The higher chances to have a successful trial if we keep the delta low enough to be very plausible.

The scientific community and other forces of the society have ambivalent positions on these issues: on the one hand there is pressure for early approval of the new agents even in the face of preliminary data or with non-impressive additional benefit; and FDA and EMEA reacted by the accelerated approval strategy (Pazdur, Schilsky).[8,9] On the other hand, the same scientific community say that we cannot afford the use of these agents for the relatively little gain in overall survival offered in the palliative setting (Bob Meyer NEJM 2004).[10]

The solution seems straightforward: to raise the currently accepted bar for the target delta in planning comparative trials in the palliative setting of most common solid tumours. In this way, we will not have to face the situation of a new host of expensive compounds with marginal efficacy approved on the basis of large scale randomised trials showing statistically significant improved efficacy over standard treatment[11] (Moore). Shifting the priority onto the second question, 'how worthwhile this difference is going to be', and thus using a higher delta to make the new treatment worthwhile has a major limitation: that we will be able to approve only highly active compounds, but may miss the cumulative effect of incremental improvements of other agents producing less spectacular results by themselves, but that results in a clinically meaningful improvement in outcome. Colorectal cancer treatment is probably the best example of this.

5. Conclusion

We are definitely making progresses in the clinical management of cancer. The progresses regard all aspects, from prevention to care and cure. Some solid tumours have improved their prognosis in a substantial way, some others are much more resistant to all our efforts. The future reserves to us a more complex scenario in terms of classification of tumours as well as a more rational, individualised approach to treatment choice. The key is moving away as soon as experimental and clinical data allow from the present paradigm where we are using and developing 21st century drugs based on a 20th century trial design and a 19th century tumour classification.

Conflict of interest statement

The authors state no conflict of interest with other people or organisations that could inappropriately influence their work.

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