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Targeted Therapies and Survival: What We Can Learn from Studies in Advanced Renal Cell Carcinoma

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For many years, the therapeutic approach to patients with advanced/metastatic solid tumors has represented a huge and frustrating challenge for oncologists since the several conventional antineoplastic agents used to treat such a patient population, even though tested according to different doses, schedules and combinations, ultimately failed to achieve significantly prolonged survival. Indeed, although the vast majority of these attempts have been able to increase the response rate and delay the time to progression to some extent, thus offering more or less consistent periods of amelioration of patients' quality of life, the impact of these benefits on survival remained inadequate without substantially modifying the natural history of the disease.

Later, advances in the understanding of the molecular biology underlying the pathogenesis of many tumor types have revealed genetic and molecular impairments resulting in an increased activity of intracellular pathways and functions related either to cell proliferation or to angiogenesis, thus disclosing new perspectives for the treatment of these diseases. Complex signaling networks in large part mediated by growth factors, such as EGFR amplified or hyperexpressed in a variety of tumor cell types, or deriving from the inactivation, mutation or deletion of certain genes (e.g. *TP53*, *PTEN*, and *ALK*), led to the possibility to treat with specific targeted therapies selected subgroups of patients bearing such abnormalities, in this way achieving substantial survival improvements as it appears from the undeniable results obtained in HER2+ advanced breast cancer patients or in KRAS+ non-small cell lung cancer patients [1].

Similar and maybe even more important considerations can be made concerning advanced/metastatic renal cell carcinoma (m-RCC). Following the explosion of information regarding the molecular basis of this tumor formerly considered refractory to any conventional chemotherapeutic systemic treatment, except for a very restricted cohort of patients responsive to cytokines, several tyrosine-kinase and other pathway inhibitors clearly proved their efficacy, chiefly through a disease progression slowdown, thus becoming the mainstay of treatment of m-RCC. However, whereas on the one hand the possibility of a disease control can be considered an extremely important achievement, on the other hand there is still a long way to go in order to better characterize, weigh and differentiate the real efficacy of these agents. In this regard, analyzing the data of the pivotal randomized studies carried out for the development of the four tyrosine-kinase inhibitors presently on the market, it immediately appears that, on the basis of intent-to-treat analyses, in no case a superiority in terms of overall survival (OS) as compared to the reference arm was proven. The majority of

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these studies, undertaken against either cytokines or placebo, fixed progression-free survival (PFS) as primary endpoint, putting OS as secondary endpoint. The reasons justifying such a choice can be mainly identified in (1) the shorter duration required to reach the evaluation of PFS as compared to OS; (2) the assumption that PFS could unquestionably be considered as 'surrogate' endpoint of OS, and the awareness that the Regulatory Authorities accepted this evaluation, and (3) the fear that the failure of an ambitious primary endpoint such as OS could compromise the outcome of the whole investigation. Besides, other issues including studies not always correctly designed and, chiefly, the interference of ethical principles requiring protocol amendments allowing the crossover of patients to the most efficacious treatment arm with consequent distortion of OS estimate must be taken into serious consideration. Attempts have been made to overcome this issue. For instance, the phase 3 randomized controlled trial of sunitinib versus interferon-α (IFN) demonstrated a significant advantage in terms of either response rate and PFS [2]. Median OS with sunitinib was greater than with IFN (26.4 vs. 21.8 months, respectively; HR = 0.821, p = 0.051) based on the primary analysis of the unstratified log-rank test (p = 0.013 using the unstratified Wilcoxon test), with a HR = 0.818 (p = 0.049) by stratified log-rank test [2]. The confounding effects of crossover on OS in this study have supported the activation of post hoc analyses to eliminate this issue [2]. As a proof of that, when the subgroups of patients who did not receive any post-study cancer treatment were analyzed separately, median OS was 28.1 months with sunitinib compared with 14.1 months with IFN (HR = 0.647, p = 0.003). The authors concluded that the survival endpoint may have been confounded by crossover treatment and/or use of post-study anticancer treatment after discontinuation [2]. Additionally, based on comparisons with historical controls with cytokine treatment, the survival data in this trial highlight improvement in the overall treatment landscape for RCC in the era of targeted therapy.

To explain the possible correlation between PFS and OS and to eliminate the confounding effect of crossover or subsequent therapies, the authors suggest to use various statistical techniques including Wilcoxon's test, which could be one of the most appropriate one when the death ratios between the two treatment groups are not constant over time and in situations where survival data may be confounded [2].

The combination regimen bevacizumab + IFN showed a statistically significant increase of PFS in two randomized phase 3 trials called AVOREN and CALGB, as compared with IFN alone [3, 4]. Both trials were designed to evaluate an improvement in OS but failed to demonstrate this. Given the potential confounding effects of subsequent anticancer therapy on OS, a post hoc analysis in the CALGB and AVOREN trial was performed [3, 4]. Notably, patients who received subsequent therapy had a better median OS compared with those who did not. A retrospective subgroup analysis of the AVOREN trial suggests that the IFN dose can be reduced to manage side effects while maintaining efficacy in patients with m-RCC receiving bevacizumab + IFN.

The confounding effects of crossover were also observed in other investigations such as the ones evaluating pazopanib and the m-TOR inhibitor, everolimus.

The RECORD-1 trial was a randomized double-blind phase 3 trial comparing everolimus versus placebo in a population with m-RCC pretreatment with at least one targeted therapy. The main goal was PFS, while secondary endpoints were OS and response rates. In this trial, a statistically significant improvement in PFS was reported, which was not associated with a benefit in OS in favor of the everolimus arm [5].

Indeed, the median OS was 14.8 (everolimus) versus 14.4 months (placebo) (HR = 0.87, p = 0.162), with 80% of patients in the placebo arm crossing over to everolimus. By the rank-preserving structural failure time model, the survival corrected for crossover was 1.9-fold longer (95% CI 0.5–8.5) with everolimus compared with placebo only [5].

Concerning the latter point, the 'road to registration' of the pivotal study carried out with sorafenib appears paradigmatic, since it fixed OS as primary endpoint. In this placebo-controlled trial, a preplanned ongoing interim analysis showed a statistically significant advantage of sorafenib over placebo in terms of median PFS ($p < 0.001$): consequently, a protocol amendment claimed by the Regulatory Authorities on the basis of ethical principles and consisting in blindness suppression in order to allow also patients of the placebo group to benefit from the active treatment with sorafenib was applied (crossover). But this justified amendment completely marred the possibility of a correct evaluation of OS: in fact, at the first analysis carried out 6 months after the crossover, median OS was still significantly in favor of sorafenib (p = 0.02), but afterwards, not in agreement with the predefined significance limits fixed by the study (p = 0.0094), at the final analysis, any superiority of sorafenib over placebo was completely extinguished (p = 0.146) [6].

Also study design and a correct and realistic choice of the doses of reference drugs appear extremely important

to avoid gross mistakes or bias. So far, the study evaluating the m-TOR inhibitor, temsirolimus, has been the only one showing a statistically significant superiority over IFN in terms of both PFS and OS in a population with poor risk and treatment naïve [7].

Recently, a randomized phase 3 trial called AXIS was undertaken in a population refractory to a previous therapy including sunitinib, cytokines, bevacizumab or temsirolimus, to compare axitinib with sorafenib. A significant improvement in median PFS was reported in the entire study population in favor of the axitinib arm versus the sorafenib arm (6.7 vs. 4.7 months, respectively; HR = 0.665). The last analysis did not show any difference in terms of OS in either experimental group (axitinib or sorafenib) nor in the preplanned analysis of sunitinib-pretreated patients [8].

Another phase 3 trial called INTROSECT compared sorafenib with temsirolimus in a population refractory to sunitinib. The study has not yet been published, but a press release underlined that there was no difference in PFS in the two arms of therapy and a trend in OS in favor of sorafenib [9].

More recently, the results of the TIVO-1 study were presented at the 2012 ASCO meeting. In this trial, tivozanib compared to sorafenib turned out better in terms of PFS in a population with untreated m-RCC or refractory to cytokines. No data in terms of OS are available up to now [10].

Given that only limited evidence of survival achieved with the different targeted agents presently available exists, nor any other definite efficacy data able to differentiate them, often, physicians are in an awkward situation concerning treatment choice: indeed, they can only and questionably rely upon the drug they deem better tolerated on the basis of its safety profile in relation to patients' clinical features and the comorbid picture. In such a situation, a reassessment of characteristics of targeted agents for the treatment of m-RCC becomes a medical need that cannot be postponed and a fundamental goal that cannot be given up. Well-designed head-to-head clinical trials comparing the available targeted agents should reconsider the role of PFS and its possible impact on survival: the existing differences, most likely apparent, of PFS values observed in clinical trials carried out in comparison with placebo or immunotherapy cannot be considered final scientific evidence as they derive from single experiences not comparable in terms of patient selection, such as previous treatment, patients' risk factors at baseline, metastatic sites, etc. At present, we are waiting for the results of a head-to-head trial named COMPARZ comparing pazopanib with sunitinib as first-line treatment in m-RCC having as its main goal the non-inferiority of pazopanib in terms of PFS. Additionally, another trial called RECORD 3 was designed to evaluate which sequence is better when sunitinib and everolimus are used sequentially at failure of a first agent.

To get ahead and to try to leave this 'grey area' which, as Chris Ryan stated at the ASCO 2010, at the moment makes all the current targeted agents for the treatment of m-RCC indistinguishable in terms of efficacy, physicians should consider some essential questions: (1) are the current targeted agents able to induce statistically significantly different PFS, and (2) if yes, is there a linear correlation between the extent of PFS and survival so that PFS could be considered a predictive factor for a better clinical outcome?

We trust that we are dealing with extremely important queries. In fact, after the initial breakthrough achieved about 10 years ago, demonstrating that a systemic treatment is able to temporarily control an orphan disease such as m-RCC, the perspective to identify the most efficacious agent or the best modality of interaction between them in order to obtain a survival prolongation represents a further important achievement. And our wish is that such an achievement will not simply remain a wishful thinking.

Disclosure Statement

All authors have no conflicts of interest.

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