Antiangiogenic tyrosine kinase inhibitors in non-small-cell-lung cancer: lights and shadows

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The MONET-1 prospective, multicenter randomized trial evaluating whether motesanib, a selective oral inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3; platelet-derived growth factor (PLGF) receptor and Kit, when combined with a standard carboplatin/paclitaxel cytotoxic schedule improves overall survival (OS) versus the same chemotherapy alone as first-line therapy for advanced non squamous non-small-cell-lung cancer reported by Scagliotti *et al.* (1) is well-conducted, evaluated and reported. The study enrolled a total of 1,090 patients and found that motesanib did not significantly improve OS over carboplatin/paclitaxel alone, even though it significantly improved median progression-free survival (PFS) and overall response rate but with the price of more high grade toxicities, namely neutropenia, hypertension, arterial thromboembolism, hemorrhagic events and cholecystitis.

The authors (1) concluded that the study was negative because the primary end-point, OS, was not reached by statistical analysis. On the other hand, motesanib improved both response rate and PFS proving that it is active in a proportion of the treated patients, suggesting that the overall effect on OS may be diluted by both primary unrecognized insensitive tumors and second-line treatments being the median OS in excess of 1 year.

Subgroup analysis indicated longer OS for non-white patients (HR, 0.76) or those enrolled outside of the USA/Canada/Australia/European Union (HR, 0.77).

Among the patients in the motesanib arm who had evaluable PLGF samples at baseline, this biomarker was not associated to outcome.

The MONET 1 trial results agree with data of other Phase III trials similarly designed, all showing no significant benefit from the addition of the multi-targeted TKIs sorafenib or vandetanib to chemotherapy in NSCLC (2-5).

Consequently, the central question is whether the study design strategy of such trials is right or not.

The strategy to add TKIs to standard chemotherapy in phase III trials in unselected patients with NSCLC was first tested with the availability of the anti-epidermal growth factor receptor (EGFR) gefitinib. The two trials, INTACT-1 and INTACT-2 (6,7) performed in large cohorts of patients, reported negative results on OS since 2004. This phenomenon even if known for several years was followed by a number of more recent studies built with the similar unsuccessful study design. Only a few years later did it become clear that only those patients with tumors bearing EGFR mutations gained benefit of gefitinib monotherapy (8). This knowledge has two important implications: the first, that the rational selection of patients is the key to obtain successful therapeutic results with TKIs therapy and second, that the combination of TKIs with standard chemotherapy in unselected NSCLC patients even in large Phase III trials without accurate pharmacokinetics and pharmacodynamic preliminary studies may lead to negative results.

Compelling evidence suggests that NSCLC should be considered as a heterogeneous tumor characterized by a number of biologically distinct diseases each with low frequency expression of mutually exclusive, potentially druggable targets.

Furthermore, immunohistochemical studies aimed to define the angiogenic patterns of NSCLC suggested that

not all tumors present neo-vascularization, therefore, some tumor subtypes are likely not to be responsive at all to antiangiogenic treatments (9).

In conclusion, the negative results reported for the MONET 1 as well as for similar trials may be explained by at least 5 factors: (I) the typical tumor heterogeneity of NSCLC inclusive of subsets without a pattern of evident neo-vascularization; (II) the pharmacodynamics of TKIs that induce G_1 cell cycle arrest, thus interfering with the cycle-dependant activity of cytotoxic agents (8); (III) in metastatic disease other pro-angiogenic factors may be in play beside those targeted by motesanib; (IV) the lack of available standardized predictive indicators for activity of antiangiogenic TKIs and finally; (V) the incapability to rationally select the patients who are more likely to benefit of therapy.

How can the therapeutic paradigm be changed to improve the efficacy of antiangiogenic TKIs agents?

The first step is to perform Phase 0 studies aimed to prove in humans that the antiangiogenic agent is capable to interfere with a step of the complex pathways leading to neo-vascularization by direct (target-mediated) or indirect mechanisms. The above preliminary study should also identify potential predictive biomarkers or dynamic imaging tests aimed to identify sensitive or primary resistant tumors. Then, Phase I studies are to be performed with the agent given as monotherapy and/or in combination with active cytotoxics or targeted agents to assess toxicity and side-effects.

Subsequent development is aimed to evaluate whether, in randomized Phase II studies, the patients selected by predictive biomarkers gain benefit in terms of response rate and PFS over standard therapy. Only positive results on activity, tolerability and the proof of the identification of potentially responsive patients should allow the involvement of a large cohort of cases in Phase III trials (10-12).

The above step-by-step study-design strategy is a way to avoid in future years the exposure of large number of unselected cases in Phase III trials with high probability of failure of the primary end-point by using antiangiogenic TKIs agents alone or in combination with other targeted agents or chemotherapy.

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