

The TOPICAL study should be more topical!

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The TOPICAL study - a prospective randomized study of first line therapy with erlotinib versus placebo in patients with advanced NSCLC, who were unfit for (standard) chemotherapy, was recently published by Lee *et al.* (Lancet Oncology, October 16, 2012) (1). The study was performed in patients with PS \geq 2. The best therapy for this prognostic unfavorable group of patients has for decades been discussed, and many comparative studies performed; doublet chemotherapy versus single agent chemotherapy, EGFR TKI versus chemotherapy etc. Most widely used for this group of patients is single agent chemotherapy. However, the average age of the patients in the TOPICAL study was 77 years, and most of them with significant comorbidities. Thus, an effective systemic therapy with fewer side effects would be an attractive option. However, no difference in the overall survival (OS) was seen with erlotinib therapy compared to placebo with a median OS of 3.7 versus 3.6 months (HR=0.92). A statistically significant prolonged progression free survival (PFS) was achieved with erlotinib with a median of 2.8 months compared to 2.6 months with placebo (HR=0.80, 0.63-0.93, P=0.0054). The question is whether such a marginal PFS difference is clinically meaningful. The study included quality of life (QOL) assessment and symptomatic assessment, and the patients treated with erlotinib had a significantly improved QOL for 2 of 5 functional scales and for 6 of 18 symptoms. Thus, with all the difficulties related to QOL- and symptomatic assessments, particularly in this group of patients and in such a multicenter setting, some clinical benefit- and not only statistical benefit- was observed in the erlotinib treated arm. The study did also observe a significant better survival for erlotinib therapy (HR=0.24, 95% CI: 0.16-0.35) in the patients, who developed skin rash during the first cycle of erlotinib therapy, which is in harmony with previous

results in younger patients treated with either EGFR TKI or cetuximab. Not surprisingly, the subgroup of patients with the best outcome was the small subgroup (7%) with tumors harboring EGFR mutations with a median OS of 10.4 months with erlotinib versus 3.7 months with placebo and a median PFS of 4.8 versus 2.9 months with placebo.

While this study clearly supports EGFR TKI therapy for the patients with tumors harboring EGFR mutations, a clinically relevant question is whether there is a subgroup of the chemotherapy unfit patients with EGFR wild type (wt) tumors, who would also benefit from erlotinib therapy as first line treatment. The TOPICAL study showed that patients with EGFR wt tumors, who developed skin rash (N=94 patients) within the first cycle had an OS HR of 0.86 (95% CI: 0.66-1.12) compared to 1.28 (95% CI: 0.95-1.72) for those patients with EGFR wt tumors and no rash. The PFS HR was for the same groups 0.69 (95% CI: 0.53-0.90) and 1.05 (0.78-1.41). Thus, a significant PFS benefit was observed with erlotinib in the group of patients with EGFR wt and skin rash during the first cycle of therapy.

However, despite some improvement in clinical outcome and QOL assessments with erlotinib in both the patients with tumors harboring EGFR mutations as well as in subgroup of patients with wild type tumors, the results from the TOPICAL study strongly call for a careful selection based on EGFR mutation status to EGFR TKI therapy also in the chemotherapy "unfit" group of patients, although, erlotinib could be an option in EGFR wild type patients, particularly if they develop skin rash during the first cycle of therapy (EGFR therapy should be discontinued if no skin rash develops). Whether any biomarkers can identify a subgroup of patients with EGFR wt tumors, who would benefit from EGFR TKIs is still an open question, which needs to be further explored in prospective studies (2).

However, it is important to acknowledge that NSCLC patient with EGFR wt tumors constitute a very biologically heterogeneous group of patients with many different potential drug targetable molecular features. Today, we know that some of the molecular characteristics have led to approved therapy options, i.e., patients with ALK-gene rearrangements. In the “near” future, we can expect more targeted agents including other molecular targets, which most likely will be suitable also in the chemotherapy “unfit” patients.

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