Editorial

Impact of performance status and age on osimertinib efficacy in patients with *EGFR*-mutant T790M-positive non-small-cell lung cancer

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Activating epidermal growth factor receptor (*EGFR*) mutations are reported in 30–40% of Asiatic patients and in 10–15% of unselected Caucasian patients with advanced non-small cell lung cancer (NSCLC) (1).

Over the last decade, patients with NSCLC and sensitizing *EGFR* mutation have been treated preferentially with first- and second-generation EGFR tyrosine kinase inhibitors (TKIs), that excelled over chemotherapy in large randomized phase III clinical trials (2-5). However, virtually all patients treated with either first- or second-generation EGFR-TKIs develop acquired resistance to treatment, which is mediated in ~60% of cases by the development of the Thr790Met (T790M) gatekeeper mutation in the exon 20 of the *EGFR* gene (6). Osimertinib mesylate is a pyrimidine-based irreversible third-generation EGFR-TKI, selective for both *EGFR* TKI-sensitizing mutations (exon 19 in-frame deletion or the L858R point mutation) and the T790M mutation, with high central nervous system (CNS) penetration and activity (7,8). In the AURA 3 trial, osimertinib demonstrated improved efficacy in patients with T790M-positive advanced NSCLC progressing after first-line EGFR-TKIs compared to conventional platinum-based chemotherapy, with a median progression free survival (mPFS) of 10.1 *vs.* 4.4 months (P<0.001) and an overall response rate (ORR) of 71% *vs.* 31% (P<0.001), respectively (9). This study established osimertinib as the best treatment option for *EGFR*-mutant T790M-positive NSCLCs who progress on first- or second-generation EGFR-TKIs.

Although the sequential treatment with a first- or second-generation EGFR-TKI followed by osimertinib provides for unprecedented survival outcomes, in the more recent phase III FLAURA trial, osimertinib also excelled over standard of care gefitinib and erlotinib in terms of mPFS (18.9 *vs.* 10.4 months, P<0.001) with a 54% reduction of risk for disease progression or death in treatment-naïve *EGFR*-mutant NSCLC patients (10). Based on the results of the FLAURA trial, osimertinib is currently considered the preferred first-line option for patients with *EGFR*-mutant advanced NSCLC.

The progressive aging of general population is leading to an increased number of elderly patients with newly diagnosed lung cancer. Elderly patients have often comorbidities, impaired organ function and often poor performance status (PS), with a higher risk of developing side effects (11,12). As a consequence, these populations are often excluded from clinical trials and the efficacy and safety of osimertinib in these subsets of patients are still poorly defined.

In the research article accompanying this editorial, Kato and colleagues have investigated the correlation between osimertinib efficacy, Eastern Cooperative Oncology Group (ECOG) PS and age in patients with T790M-positive advanced NSCLC treated with osimertinib after progression to standard EGFR-TKI (13).

Among 31 evaluable patients, 8 were classified as young

(age <65 years) and 23 as elderly (age ≥65 years). In the entire cohort, 10 had a ECOG PS ≥2. When clinical outcomes were evaluated according to age, the mPFS was found to be significantly shorter in young patients compared to elderly patients (3.5 *vs.* 6.4 months, P=0.041), while no significant difference in median overall survival (mOS) was observed between the two cohorts (5.3 *vs.* 19.4 months, P=0.067), suggesting that resistance may occur earlier in younger patients. The lack of OS benefit could be partly explained by the fact that elderly patients are more likely to have comorbidities that might reduce the difference in terms of OS between the two groups. However, this data should be interpreted cautiously due to the small sample size.

When the clinical outcomes were analyzed by ECOG PS, the mPFS was 9.1 months among patients with good PS (ECOG 0–1) and 5.5 months among patients with poor PS (ECOG ≥2) (P=0.071), whereas OS was not reached and 6.6 months (P=0.061), respectively. The toxicity profile was manageable, with no grade ≥3 adverse events (AEs) in young patients and two cases of interstitial lung disease (ILD) in elderly patients. Three patients discontinued because of treatment-related toxicity (two in the elderly and one in the young group) and six needed a dose reduction across the overall population (five in the elderly and one in the young group).

Several studies have demonstrated high efficacy and acceptable safety profile of first-generation EGFR-TKI, such as gefitinib and erlotinib, in elderly patients with *EGFR*-mutant advanced NSCLC (14,15) whereas other studies showed that grade ≥3 toxicities are more likely to occur in this subset of patients (16,17). When it comes to osimertinib, a recent retrospective study evaluated safety and efficacy of osimertinib in patients with *EGFR* T790M-mutant advanced NSCLC, according to age (18). Among 77 evaluable patients, 59 (77%) were young (defined as <75 years), whereas 18 (23%) were elderly (≥75 years). This study showed no significant differences between the two groups in terms of ORR (50.8% in young *vs.* 61.1% in the elderly cohorts, P=0.59), mPFS (10.5 *vs.* 17.7 months, respectively, P=0.11) and OS (38.6 months *vs.* not reached, P=0.20, respectively). In addition, the safety profile was overall similar between the two age groups: grade ≥2 thrombocytopenia was the most common AE in both groups, while grade ≥2 paronychia was more commonly observed in the elderly cohort.

Of note, a prospective, single arm, phase II trial specifically investigated efficacy and safety of osimertinib in elderly patients (age ≥75 years) with T790M-positive advanced NSCLC (19). Among the 36 enrolled patients, ORR was 58.3%, median duration of response (mDOR) was 27.9 weeks and disease control rate (DCR) was 97.2%, with any tumor shrinkage occurring in 91.6% of patients. The safety profile was acceptable, with most common AEs being decreased appetite (38.9%), diarrhea (36.1%), rash (33.3%) and paronychia (33.3%).

Why median PFS should be longer in elderly patients?

One possible explanation may lie in the different TKIs metabolism in elderly patients due to residual organs function and interactions with other medications, that might increase TKIs plasma levels (16,20). This may be consistent with the higher efficacy and greater toxicity reported in elderly patients (21).

Another factor that should be considered is the higher prevalence of uncommon *EGFR* mutations (e.g., exon 18 and exon 20 mutations) in younger patients, that are known to be less sensitive to EGFR TKIs when compared to "classical" *EGFR* mutations (e.g., exon 19 deletions and L858R point mutation) (22,23). Importantly, a Korean study showed that osimertinib is highly active and produces durable responses in NSCLC patients harboring uncommon *EGFR* mutations with a manageable safety profile (24). However, it should be highlighted that the ORR (50%) and the mPFS (9.5 months) in the overall population of this study were inferior to the outcomes to osimertinib reported in the FLAURA trial (10).

Notably, in the study by Kato and colleagues all the uncommon *EGFR* mutations occurred in the elderly cohort, which seems surprising as this group had better outcomes to osimertinib compared to the young cohort. More importantly, younger patients were more likely to have exon 21 mutations, brain metastasis at baseline and to be heavily pretreated. Therefore, it can be argued that the better outcomes observed in the elderly cohort may reflect an overall imbalance in these characteristics, rather than a predictive value of age. Accordingly, no difference in osimertinib efficacy according to age was observed during the drug developmental program (e.g., AURA phase II expansion cohort, AURA 3), suggesting a limited, if any, impact of age in predicting osimertinib efficacy

and highlighting that small retrospective series should be interpreted with caution.

What about PS?

Patients with poor PS are often excluded from clinical trials but also from conventional therapies and are usually candidate to best supportive care alone. EGFR-TKI therapy may be considered an exception since *EGFR*-mutant patients with poor PS treated with EGFR-TKIs often experience a dramatic improvement in tumor burden and consequently in PS, leading to the so-called "Lazarus Effect", with an acceptable toxicity profile (15). A phase II study of gefitinib in *EGFR*-mutant NSCLC patients not candidate to chemotherapy (poor ECOG PS or ≥80 years old) reported an ORR of 66% and a mPFS of 6.5 months (15). Overall, PS improvement was reported in 23 patients (79%), and 22 (68%) of those with a PS of 3–4 experienced an improvement to a PS <2.

More recently, a retrospective Japanese study investigated efficacy and safety of osimertinib in 30 patients with *EGFR* T790M-positive advanced NSCLC and poor ECOG PS progressing after first-line EGFR-TKIs. Among them, 24 patients (80%) had a PS of 2, 6 (20%) had a PS of 3, while none had a PS of 4 (25). ORR and mPFS were 53% and 8.2 months, respectively, with no difference in mPFS between patients with a PS of 2 and those with a PS of 3 (P=0.35). Overall, PS improved in 19 (63%) patients, including four patients with a PS of 3 (67%) improving to a PS <2. In this study osimertinib resulted to be well tolerated, with no new safety concerns. Although these outcomes appear inferior to what reported in clinical trials exploiting EGFR-TKIs activity in similar settings, it should be highlighted that these patients were usually excluded (9,10), as a poor PS is a well-known prognostic factor in cancer.

Certainly, the small sample size of these studies does not allow to control for possible confounding factors, and a poor PS has to be considered a prognostic rather than predictive factor of response to osimertinib.

Conclusions

Available evidence indicates that PS and age cannot be considered as predictive biomarkers of osimertinib response. Rather, PS and age are well-known prognostic factors in cancer patients across different tumor types and treatments. Larger real-life studies are needed to investigate whether age and PS impact clinical outcomes to osimertinib in patients with *EGFR*-mutant T790M-positive NSCLC and in which way.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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