Editorial

# Impact of clinical features on the efficacy of osimertinib treatment in epidermal growth factor receptor mutant non-small cell lung cancer patients with acquired resistance to tyrosine kinase inhibitors due to T790M mutation

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Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are the treatment of choice for patients with advanced stage non-small cell lung cancer (NSCLC) harboring EGFR sensitizing mutations (1,2). Before osimertinib, a third-generation EGFR-TKI, is recommended as the preferred agent in the first-line treatment in these patients, earlier generation TKIs such as erlotinib, gefitinib and afatinib, were the drug options available. After a median treatment duration of 9 to 11 months, resistance to these first- or second-generation EGFR-TKIs invariably occurs. In 50–60% of cases the resistance mechanism is the acquired *EGFR T790M* mutation in exon 20 where threonine at amino acid position 790 is substituted with methionine (3,4). Osimertinib is designed to inhibit *EGFR T790M* mutation while also having inhibitory activity on sensitizing *EGFR* mutations (5). Following the positive results of the Phase III AURA3 randomized controlled trial which show the superiority of osimertinib over platinum and pemetrexed chemotherapy in the treatment of patients with *EGFR* mutant advanced NSCLC after failure of front-line therapy with EGFR-TKI due *T790M* mutation (6), osimertinib has been approved for this indication (1). In the AURA3 trial, the median progression-free survival (PFS) of patients treated with osimertinib was 10.1 months which was significantly longer compared to the median PFS of 4.4 months in those treated with chemotherapy (6). Compared to chemotherapy, osimertinib treatment resulted in a significantly better objective response rate (ORR) of 71% versus 31% and a significantly longer median duration of response (DoR) of 9.7 versus 4.1 months.

Since then, there has been a growing interest to determine if certain subsets of patients with different clinical features benefit from osimertinib treatment more than others which may guide treatment options and selection. Previous studies have identified age, Eastern Cooperative Oncology Group performance status (ECOG PS), gender, smoking status, *T790M* mutation positivity by liquid biopsy, and central nervous system (CNS) metastasis as prognostic features of patients treated with EGFR-TKIs (7-9).

The results of a single-center retrospective real-world study in Tokyo, Japan conducted by Kato and colleagues which analysed the impact of age, ECOG PS, and other clinical parameters on the treatment outcomes with osimertinib in *T790M*-positive NSCLC were published in an earlier issue of this journal (10). Of a total of 31 NSCLC patients with acquired resistance to first-or second-generation EGFR-TKIs due to *T790M* mutation treated with osimertinib between March 2016 and January 2018, 24 (77.4%), 5 (16.1%), and 2 (6.5%) patients were treated with first-line first-or second-generation EGFR-TKIs, gefitinib, erlotinib, or afatinib, respectively. The ORR for

the 31 patients was 53.3% and was not significantly different between the groups stratified according to age younger than 65 years and at least 65 years, or good ECOG PS of 0–1 and poor ECOG PS of 2–4. Fourteen (45.2%) patients had CNS metastases at the start of osimertinib treatment. Multivariate analysis showed that age and ECOG PS were independently predictive of osimertinib efficacy. The authors concluded that osimertinib is less efficacious in *EGFR* mutant NSCLC patients who fail first- or second-generation EGFR-TKI and positive for *T790M* mutation with poor ECOG PS (2-4) and age younger than 65 years (10).

With a median follow-up duration of one year, the median PFS and median overall survival (OS) were 5.6 [95% confidence interval (CI), 3.6–14.8] months and 19.4 (95% CI, 9.1–not achieved) months, respectively. The shorter PFS and OS of patients treated with osimertinib this real-world retrospective analysis compared with that reported previously by clinical trials (6,11,12) could have been due to a high proportion (32.3%) of patients with poor ECOG PS) in this study. In general, poor ECOG PS is associated with poorer survival in patients with NSCLC. In another real-world study, poor ECOG PS is a predictor of poor OS in patients with advanced NSCLC with sensitizing *EGFR* mutations treated with first-line gefitinib (7). Clinical trials only enroll patients with good ECOG PS of 0-1 but in the real world, patients with poorer ECOG PS are not uncommon and need to be treated as well.

In this real-world study by Kato and colleagues, 10 (32.3%) patients had poor ECOG PS scores of 2–4. These patients with poor ECOG PS had shorter PFS and OS despite responding well to osimertinib (10). The median PFS of patients with poor ECOG PS was 5.5 months while that of patients with good ECOG PS of 0–1 was 9.1 months [P=0.071; hazard ratio (HR), 0.38] but the difference was not statistically significant. Similarly, the OS of patients with poor ECOG PS was numerically but not significantly shorter than that of those with good ECOG PS (6.6 months *vs*. not reached, P=0.061; HR, 0.39).

In this study, 8 patients were younger than 65 years and 23 were aged 65 years or older (10). The age cut-offs of younger than 65 years and 65 years of older were similar to those used in the AURA3 trial subset analysis (6). The median PFS of patients younger than 65 years was 3.5 months which was significantly shorter than that older patients which was 6.4 months (P=0.041; HR, 2.41). The median OS was numerically but not statistically significantly shorter in the younger patients than the older patients (5.3 *vs*. 19.4 months, P=0.067; HR, 2.58).

The results of the limited number of studies on the effect of age on EGFR-TKI treatment have not been consistent. One prospective phase II study demonstrated similar efficacy and safety of erlotinib in older and younger patients (13). A study by the Taiwanese group led by Yao et al. who analysed 226 patients found no significance PFS difference related to age groups when treated with first- and second-generation TKIs (7). A meta-analysis focusing on the relationship of age and first- or second-generation TKI used (gefitinib, erlotinib, and afatinib) most notably did not show any difference in EGFR-TKI efficacy between patients age 65 years or younger and patients older than 65 years (14). In a larger cohort of 1656 Japanese patients, age younger than 75 years and good ECOG PS are found to be significant favorable predictors of OS (15). However, in another study, first- or second-generation EGFR-TKIs was less effective in patients younger than 50 years than in older NSCLC patients (16).

The mechanistic reason why EGFR-TKIs are less efficacious in younger patients is unknown. An earlier study shows a higher frequency of uncommon mutations in young patients (16) and this may explain the poorer prognosis of younger patients who are treated with first-generation EGFR-TKIs. The response rate is lower and PFS is shorter with EGFR-TKI treatment in patients with uncommon *EGFR* mutations compared to patients with exon 19 deletion or L858R mutation (17,18). However, osimertinib has been demonstrated to be effective against some uncommon mutations (19). In a phase II multicenter single arm study of osimertinib in NSCLC patients whose tumors harbor uncommon *EGFR* mutations comprising of G719A/C/D/S/X in 19 patients, L861Q in 9 patients, S7681 in 8 patients, and others in 4 patients, the ORR was 50.0% (95% CI, 32.8–67.2%) and disease control rate (DCR) was 88.9% (95% CI, 78.1–99.7%) (19). Partial response was observed in seven patients (77.8%) with L861Q mutation; 10 (52.6%) with G719A/C/D/S/X mutation; and three (37.5%) with S768I mutation. The median PFS was 9.5 months (range, 1.0–20.1 months) and median DoR was 7.0 months (95% CI, 4.7–9.3 months). In this study by Kato and colleagues, only two patients had uncommon mutations and both the patients were aged 65 years or older. Therefore, uncommon mutations were not responsible for the lower efficacy of osimertinib in the younger patients in this study.

While the clinical features of patients younger than 65 years and older patients were not significantly different, a higher proportion of patients aged 65 years or older (65.2%) than those younger than 65 years (50.0%) had

 

exon 19 deletion mutation which is associated with a better response (20) and predicts longer PFS and OS when treated with salvage osimertinib (20,21). In a prospective observational cohort study on the efficacy and safety of osimertinib in 51 patients with *EGFR* mutant advanced NSCLC whose disease had progressed on first-line EGFR-TKI therapy and who harbor the *T790M* resistance mutation, the response rate in patients with exon 19 deletion was significantly higher (69.7%) than that in patients with L858R point mutation (38.9%) (20). The median PFS in the exon 19 deletion group was also significantly longer (8.0 months) than in the L858R point mutation group (5.2 months). The median OS in the exon 19 deletion group (19.8 months) was significantly longer than L858R point mutation group (12.9 months). Exon 19 deletion mutation was an independent predictor of longer PFS and longer OS on multivariate analysis. In a retrospective multicenter review, Auriac *et al*. reported significantly longer PFS and OS with osimertinib treatment in *T790M*-positive advanced NSCLC patients with exon 19 deletion than in those with L858R point mutation who were pretreated with first- or second-generation EGFR-TKI (21). The median PFS was 13.5 and 9.7 months in patients with exon 19 deletion and exon 21 mutation, respectively while the median OS was 23.1 and 15.3 months in patients with exon 19 deletion and exon 21 mutation, respectively. In the FLAURA study, first-line osimertinib treatment is associated with a numerically longer PFS in patients with exon 19 deletions (21.4 months) than in those with L858R mutation (14.4 months) (22).

Another possible explanation for the shorter PFS in younger patients in this study by Kato and colleagues is that a higher proportion of the younger patients (62.5% of 8 patients) had CNS metastases compared to patients aged 65 years or older (39.1% of 23 patients). The efficacy of osimertinib in treating and preventing CNS metastasis has been demonstrated by the FLAURA study on treatment naive patients with tumors harboring sensitizing *EGFR* mutations and the phase III AURA3 study on patients with *T790M*-positive NSCLC after failure of first-line EGFR-TKI treatment (22,23). However, even with osimertinib treatment the presence of CNS metastases is associated with worse outcomes as compared to those without CNS metastases. In the FLAURA study, the median PFS for patients without CNS metastases and those with CNS metastases was 19.1 and 15.2 months, respectively when osimertinib was used upfront in patients with common sensitizing *EGFR* mutations (22). The respective PFS for patients without CNS metastases and those with CNS metastases was 10.8 months and 8.5 months, when osimertinib was used in the presence of *T790M* mutation after failure of first-line EGFR-TKI in the AURA3 study (6).

What was not investigated in the study is the presence of tumor heterogeneity where the early loss of plasma *EGFR T790M* translates to a poorer PFS and OS as a result of competing resistance mechanisms not targeted by osimertinib (24). The ratio of *T790M* to *EGFR* activating mutations has also been shown to correlate with response to osimertinib in NSCLC with patients having a higher *T790M* ratio showing better response and a longer DoR to osimertinib (25).

Being a single-center study which is retrospective with a small sample size, there could have been selection bias despite accounting for additional confounding factors such as gender, smoking history, histology, sensitizing *EGFR* mutation subtype, brain metastasis, and initial EGFR-TKI used which may affect the outcome in both subgroups of patients. Despite this shortcoming, the study provides useful information on the efficacy and toxicity of osimertinib in the real-world setting where unlike clinical trials older patients and those with poorer ECOG PS are also treated. Such a publication of real-world experience in the use of osimertinib in the treatment of older patients and those with poor ECOG PS provide additional evidence of the efficacy of the drug even in those with poor ECOG PS. Whether age is a predictor of osimertinib efficacy in terms of survival and response rate needs to be addressed in larger prospective studies. On the other hand, the better response and longer PFS and OS observed in the older patients could have been due to the higher prevalence of exon 19 deletion mutation in older patients. Since osimertinib response rates, PFS and OS may be impacted by the *EGFR* mutation subtype, the proportions of various subtypes of sensitizing *EGFR* mutations should be considered a stratification factor when designing clinical studies in which osimertinib is used in the first-line setting or as second-line salvage therapy after the failure of first-line EGFR-TKI.

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## Footnote

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