Research Highlight

Gefitinib NSCLC maintenance therapy

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Dr. Zhang and co-authors have demonstrated that gefitinib "maintenance therapy" of newly diagnosed east Asian non-small cell lung cancer (NSCLC) patients who were progression-free after four cycles of platinum-based doublet chemotherapy, resulted in a significant increase in progression free survival (PFS) and objective response rate without a concomitant increase in overall survival (OS).

The study design of the gefitinib trial is similar to the design of erlotinib and pemetrexed maintenance trials that have been approved by the United States Food and Drug Administration (1,2). The pemetrexed trial approval was limited to patients with non-squamous histology whereas the erlotinib approval included all non-small cell histologies. In these studies the median age of patients was about 60 years, the majority of patients were male and White and about 20% were never smokers. Most patients had Stage IV disease. In the erlotinib study 69% of patients were epidermal growth factor receptor (EGFR) positive by immunohistochemistry.

In the erlotinib trial the P-value for PFS in the intent to treat population was $P<0.0001$ while the P-value for overall survival was a more modest $P=0.009$. In the pemetrexed trial corresponding P-values were $P<0.00001$ for PFS and $P=0.012$ for OS.

The following issues impact the interpretation of the aforementioned maintenance trials: (I) the most appropriate study design; (II) the appropriate efficacy endpoint; (III) whether the risk to benefit relationship is favorable or not; and (IV) for EGFR targeted drugs the need for an approved companion in-vitro diagnostic.

What a maintenance trial ideally should be testing is whether immediate treatment after 4 cycles of chemotherapy is superior to delayed treatment started at the time of disease progression. If this is the case then the same regimen must be used for both patient groups. Neither the two FDA approved trials nor the present gefitinib study used this design. In the pemetrexed trial 67% of patients randomized to the placebo arm received post-progression second-line chemotherapy. Of these patients only 27% received pemetrexed the remainder receiving other U.S. FDA approved second-line drugs including docetaxel, erlotinib or gefitinib, gemcitabine and vinorelbine. Similarly in the erlotinib maintenance study of the 57% of placebo treated patients who received post-progression second-line chemotherapy only 14% received erlotinib or gefitinib. In the present gefitinib report 62% of placebo treated patients received post-progression chemotherapy and only 29% received targeted drugs, Thus none of the aforementioned trials adequately tested the worth of maintenance chemotherapy.

As regards the appropriate primary efficacy endpoint all studies used PFS. If one considers the hypothesis underlying the maintenance concept that early therapy when the tumor burden is reduced is superior to delayed therapy after tumor regrowth then OS is the appropriate endpoint. The fact that all trials showed a greater effect on PFS than on OS is troublesome.

Patients receiving immediate treatment are at greater risk for drug related adverse events than are placebo treated patients. Adverse events may result in hospitalization, the need for blood product transfusion and, in extreme cases, to death. Treatment toxicity must be considered when evaluating the risk to benefit relationship of a proposed maintenance treatment regimen.

When conducting studies with EGFR targeted agents the need for a companion diagnostic to detect exon 19

deletions, exon 21 L858R point mutations or mutations or deletions in other exons of the tyrosine kinase domain of the EGFR is essential for maximizing treatment benefit. No such devise has been submitted to the U.S. FDA, to date.

In summary, randomized, placebo-controlled clinical trials of maintenance therapy of NSCLC patients who have completed 4 cycles of a platinum doublet regimen without disease progression have consistently demonstrated improvement in PFS with more modest improvement in OS. The cost is increased, though usually clinically manageable, toxicity.

The most frequently stated reason for the OS results is the confounding effect of subsequent therapy of placebo treated patients. It generally is not acknowledged that patients who receive maintenance therapy may also receive additional therapy at progression. Moreover this reasoning ignores the potential benefit of treatment when the tumor burden is reduced.

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