

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Cetuximab: Potential Role as First-line Treatment for Advanced Non-Small Cell Lung Cancer

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H&O What is the mechanism of action of cetuximab and how does it differ with other first-line treatment of non small cell lung cancer (NSCLC)?

RP Cetuximab (Erbix, BMS Canada and Imclone System Inc.) is a monoclonal antibody directed at the epidermal growth factor receptor (EGFR). It attaches itself to EGFR, competitively inhibiting the binding of EGF and other ligands. In addition, it results in the internalization and degradation of the receptor, which might be one of the differences compared to EGFR directed tyrosine kinase inhibitors (TKIs). As the binding of cetuximab to EGFR blocks phosphorylation and activation of receptor-associated kinases, it consequently results in the inhibition of cell growth, induction of apoptosis, and decreased production of matrix metalloproteinase and vascular endothelial growth factor.

Its efficacy in combination with EGFR TKIs, such as erlotinib and gefitinib, is an open issue. There is no concrete evidence on whether it has a synergic effect, although it is certainly a question that is worthwhile to address.

H&O How might Cetuximab affect the prognosis of advanced NSCLC?

RP Studies with cetuximab were based on the assumption that you can increase survival by adding cetuximab

to a palliative chemotherapy, which was first suggested in a randomized phase II trial with cisplatin/vinorelbine.¹ This trial demonstrated that cetuximab increased the response rate and also suggested its potential to improve survival. Based on this, we decided to go ahead with a phase III trial—the FLEX trial. The aim of the trial was to show superior survival with the chemotherapy plus cetuximab arm compared to the chemotherapy alone arm. Based on the postulated mechanism of action of cetuximab, we decided to select patients who showed EGFR expression by immunohistochemistry (IHC), and also decided to study patients with advanced NSCLC (ie, metastatic NSCLC or stage IIIB NSCLC with malignant pleural effusion). All histologies were included and patients were randomized to receive chemotherapy plus cetuximab or chemotherapy alone. The primary endpoint was overall survival (OS). The study was able to demonstrate a statistically significant improvement in OS for the chemotherapy plus cetuximab arm, compared to the chemotherapy alone arm.² Thus this is one of the few studies that could demonstrate a benefit of a targeted treatment when added to chemotherapy in patients with advanced NSCLC.

Cetuximab added to chemotherapy also resulted in higher response rates in nearly all studies where cetuximab was combined with chemotherapy. Moreover, the benefit of cetuximab was seen with several platin-based doublets suggesting that cetuximab acts independent of the type of chemotherapy.

H&O What were the toxicity profiles that are of note?

RP The typical chemotherapy toxicities, as well as the well-characterized skin rash secondary to cetuximab, are seen in trials where cetuximab was added to chemotherapy. Other side effects of cetuximab include a slightly higher

rate of diarrhea and a low percentage of infusion-related reactions, usually without major allergic reactions. These side effects of cetuximab are well known and manageable in daily practice.

H&O Are there certain subgroups of patients who have a higher likelihood of benefiting from cetuximab?

RP Like with other targeted therapies, selection of patients who benefit is of major importance. Research focuses on protein expression, gene amplification and mutations of the EGFR receptor gene. Alternatively, clinical parameters (eg smoking status) and also the development of skin rash during treatment should be studied as potential predictors of benefit. In comparison to other cancers, however, NSCLC is a very heterogeneous and complex disease which makes the characterization of predictive markers for use in daily practice much more challenging.

H&O What do we know of markers of resistance for EGFR directed therapy?

RP We are assessing whether EGFR expression by fluorescent in situ hybridization (FISH) and/or IHC are predictive markers identifying patients that will benefit from cetuximab therapy. Our goal is to find these or other predictive markers, but such studies are ongoing and there is no clear answer at this moment. One study of note has been developed by Fred R. Hirsch, MD, PhD, of the University of Colorado Cancer Center, and his team, who have set up a trial whereby therapy is based on EGFR status of the tumor.³ In his study, FISH-positive patients had a higher response to cetuximab and chemotherapy (paclitaxel plus carboplatin) than FISH-negative patients ($P=.14$), and disease control was statistically superior for the FISH-positive group.

Patients with FISH-positive tumors had a median PFS of 6 months, whereas FISH-negative patients had a PFS of 3 months ($P=.0008$). The FISH-positive group had a median survival time of 15 months, compared with 7 months for the FISH-negative group ($P=.04$). This suggested that EGFR genomic amplification assessed by FISH may be both a prognostic factor and a predictive factor for the selection of NSCLC patients likely to benefit from cetuximab plus chemotherapy.

H&O What research do you deem necessary in the future?

RP We are awaiting the full publication of both the FLEX trial and the BMS 099 trial. Nevertheless, I do see cetuximab as a new standard option for patients with advanced EGFR-expressing NSCLC, and I see opportunities for stage III patients by adding cetuximab to chemoradiotherapy or radiotherapy. Initial phase II trials indicated that the addition of cetuximab to chemoradiotherapy is feasible and might improve the outcome in these patients. Perhaps it is a little too early to claim so, but I think that clinical trials determining the impact of cetuximab on the outcome of adjuvant chemotherapy in patients with completely resected NSCLC are warranted.

References

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