Evidence-based role of bevacizumab in non-small cell lung cancer

Palliative chemotherapy improves the quality of life and prolongs survival in patients with metastatic non-small-cell lung cancer (NSCLC). Doublet platinum-based chemotherapy has been accepted evidence-based therapy for the last two decades. Recent modifications have been the introduction of histology as a parameter defining the optimal choice of a doublet regimen and the emergence of single-agent maintenance chemotherapy for patients without progression on initial doublet therapy [1, 2]. The increasing ability to molecularly characterize NSCLC has also created much excitement. There is clear evidence that specific molecular findings, in particular, tyrosine kinase mutations or translocations can be of great value in patient selection allowing currently ~15% of patients to receive more active and less toxic targeted single-agent therapy [3]. However, a majority of patients do not have this option and continue to be offered standard doublet chemotherapy.

Attempts to increase the activity of chemotherapy in a non-selective manner have included the addition of monoclonal antibodies, in particular, antibodies directed against the epidermal growth factor receptor (EGFR) or against the vascular endothelial growth factor (VEGF). This strategy has been only marginally successful. While cetuximab, directed against the EGFR, modestly improved survival in the large randomized 'Flex' trial, other studies have been negative and in the absence of validated molecular selection criteria, its added benefit in an unselected patient population appears to be very small [4, 5]. The principles of anti-angiogenic therapy have been of laboratory and clinical interest for many years [6]. In NSCLC, the leading anti-angiogenic agent is bevacizumab. It has also been investigated in multiple other solid tumors and is part of standard therapy in colorectal cancer, gliomas and renal cell cancer. Its toxicity spectrum is well-defined. However, a search for reliable, predictive biomarkers allowing for patient selection continues [7]. In this edition of *Annals of Oncology*, Soria et al. present a meta-analysis of four randomized studies that prospectively evaluated the contribution of bevacizumab to platinum-based doublet chemotherapy [8]. A total of four trials were analyzed including two phase III studies and two randomized phase II trials. Three of the trials used a paclitaxel (Taxol)-based regimen and one used gemcitabine.

What did we know regarding bevacizumab before this meta-analysis and what new information has it provided? ECOG 4599 demonstrated longer progression-free (PFS) and overall survival (OS) with the addition of bevacizumab at a dose of 15 mg/m² every 3 weeks to carboplatin and paclitaxel [9]. Patients on the bevacizumab arm also received maintenance bevacizumab; however, the relative value of its administration with chemotherapy or as single-agent maintenance remains unknown since the two individual study components were not separately evaluated. Subset analysis suggested that older patients derived no benefit from the addition of bevacizumab [10]. In the phase III AVAiL trial, patients were treated with cisplatin and gemcitabine versus the triplet regimen with bevacizumab administered at either 7.5 mg/m² or 15 mg/m² every 3 weeks. In the initial publication, survival was not reported and increased PFS for the lower-dose arm was demonstrated [11]. A later survival analysis failed to show a survival benefit for the triplet regimen [12]. Thus, bevacizumab added to gemcitabine/cisplatin did not improve survival and the trial raised the question of its optimal dose. Of interest, only patients with non-squamous cell histology were eligible. Since then it has been established that gemcitabine is inferior to pemetrexed in non-squamous histology [1]. Thus, the trial investigated the addition of bevacizumab to a sub-optimal doublet base for its target patient population. Two randomized phase II studies are also included in the meta-analysis and evaluated bevacizumab added to paclitaxel [13, 14]. One of these (JO19907) reached statistical significance in favor of the addition of bevacizumab for the PFS end point [14]. Analyzed separately, these trials support the administration of bevacizumab with carboplatin and paclitaxel, while its administration with gemcitabine underperforms for the survival end point and is not clinically relevant since gemcitabine is preferentially given to patients with squamous cell histology who are poor candidates for bevacizumab due to risk of pulmonary hemorrhage.

In their meta-analysis, Soria et al. analyzed the above four trials using published data. It was originally intended that this summary level analysis would be followed by individual patient data but this aspect of the work unfortunately was not carried out. The meta-analysis was, therefore, based on the reported summary data, both overall and within subgroups. While the meta-analysis was generally well conducted, including the incorporation of tests for heterogeneity of the treatment effect across trials, a few points should be noted. First, none of the tests for heterogeneity reached statistical significance and therefore, only the results of fixed effects models are provided. In one trial (AVF-0757), the direction of the effect could not be discerned for the OS end point. Finally, two of the studies included high-dose and low-dose bevacizumab. Since the pooled hazard ratio (HR) is a weighted average of the HRs from the individual 'trials', the same control data appear twice in the calculation, once for the high-dose/control HR and once...
for the low-dose/control HR, and these two HRs are correlated (Imagine that, by chance, the survival rate in the control arm was unusually good. This would tend to push both HRs toward one.) While the authors down-weighted those studies to adjust for the double counting, it is not clear that this entirely corrects for the correlation and the variance of the estimate may still be underestimated.

The authors conclude that bevacizumab prolongs survival when added to first-line platinum-based chemotherapy (overall HR 0.90; 95% CI 0.81, 0.99; P = 0.03) and PFS (HR 0.72; 95% CI 0.66, 0.79; P < 0.001) which translates into a 4% survival advantage at 12 months. They also conclude that bevacizumab showed greater efficacy in patients with adenocarcinoma, and lower body weight loss, but detected no apparent interaction of the treatment effect with age.

Is the conclusion that bevacizumab added to any platinum-based chemotherapy prolongs survival supported by these data? We do not believe so and consider an evidence-based survival benefit to be limited to paclitaxel and carboplatin. The overall marginally positive statistical survival data reported by the authors are most likely explained by the fact that the large paclitaxel-based trial (ECOG) is not fundamentally disturbed by the less positive gemcitabine trial (AVAIL), while the two smaller paclitaxel-based studies contribute only marginally to the overall results. When the two large trials are analyzed together and one shows both improved PFS and OS and the other a trend for survival, it is not surprising that the overall analysis will come out ‘positive’. As discussed earlier, the paper is also diminished by the fact that individual patient data were not utilized and updates beyond those of the initial database were not carried out. The broad conclusion that bevacizumab can be added to doublet chemotherapy with a survival benefit seems exaggerated, given that only two specific doublets were examined, one in patients who would no longer be offered the drug (i.e. non-squamous cell histology treated with gemcitabine).

Recently, two additional randomized trials have provided us with new data on bevacizumab. In the ‘Pointbreak’ trial, patients were randomly assigned to carboplatin, paclitaxel plus bevacizumab versus carboplatin, pemetrexed plus bevacizumab [15]. There was no difference in OS (13.4 versus 12.6 months, respectively). Patients on both study arms continued with maintenance therapy (either bevacizumab alone or bevacizumab and pemetrexed). Exploratory analysis suggested that the doublet maintenance arm might be superior in patients who continued on trial during the maintenance treatment phase, a finding which is consistent with data from other pemetrexed-based maintenance chemotherapy trials [2]. Similarly, in the ‘AVAPERL’ trial, patients were randomly assigned to bevacizumab alone or bevacizumab–pemetrexed as maintenance following four cycles of cisplatin, pemetrexed and bevacizumab [16]. Maintenance pemetrexed significantly increased PFS and in early reporting showed a positive trend for survival.

What are some of the current questions of interest regarding bevacizumab? Does bevacizumab selectively enhance paclitaxel-based regimens? Preclinical data indicate that paclitaxel might be more susceptible to positive modulation by bevacizumab [17]. In mouse modeling of breast and lung cancers, a paclitaxel and bevacizumab combination is synergistic, potentially due to increased paclitaxel concentrations in the tumor secondary to the downregulation of vascular permeability [18]. Clinical experience has generally been less favorable in gemcitabine-based trials [19, 20]. Bevacizumab’s interaction with docetaxel (Taxotere) or nab-paclitaxel is not well established in lung cancer and will be of interest. In luciferase-tagged breast cancer mouse models with metastases to lungs, metastasis formation was decreased with nab-paclitaxel and bevacizumab when compared with each drug alone [21]. As mentioned above, any clinical interaction with gemcitabine is likely to be small. Furthermore, given the mutually exclusive indications for gemcitabine (based on activity) and bevacizumab (based on toxicity), this combination is of no clinical interest in advanced stages although there may be a role for bevacizumab with gemcitabine in resected patients where tumor-related bleeding is of less concern. Of greater clinical interest has been the interaction of pemetrexed with bevacizumab. The ‘Pointbreak’ trial seems to indicate equivalence of the two regimens; however, it does not exclude the possibility that the doublet of carboplatin and pemetrexed is as active and less toxic than either of the triplet regimens. In fact, the median survival of 12.6 months for the pemetrexed-based doublet reported by Scagliotti et al. is numerically identical to that reported by Patel et al. for the pemetrexed-based triplet [1, 15]. While more clinical data on the role of pemetrexed combined with bevacizumab and its contribution to maintenance will be needed, there appears to be little justification at this time to consider its addition to a pemetrexed-based regimen as a standard.

The role of bevacizumab in the maintenance setting remains unclear. AVAPERL and Pointbreak demonstrate an improved outcome but in both trials that effect could be attributed to pemetrexed. Both bevacizumab and pemetrexed can be administered as maintenance and it will be crucial to determine if both the drugs together truly outperform the individual drugs in that setting. Currently, ECOG 5508 is comparing maintenance bevacizumab with pemetrexed versus the combination and this study should establish the relative contributions of these two agents to improving survival [22]. The optimal dose of bevacizumab also remains unclear, although the ECOG trial using the higher dose was the only trial to show significant improvement in survival. Our recommendation at this point is to consider as evidence-based the use of bevacizumab with carboplatin and paclitaxel as established in ECOG 4599. The effect of bevacizumab on lower stage disease similarly remains unclear. This meta-analysis seems to suggest possible increased benefits in patients with stage IIIB disease, although it is not clear whether this included patients with stage IIIB disease due to advanced nodal stage or due to pleural effusion. When attempting to integrate bevacizumab with radiation complications included tracheoesophageal fistula with fatal hemoptysis and this approach is not being pursued. Bevacizumab remains of interest in the adjuvant setting as currently investigated in ECOG1505.
A number of other anti-angiogenic agents have been investigated in advanced stage NSCLC without success. Vandetanib, a small molecule inhibitor of VEGF signaling, and to a lesser extent EGFR and RET, has been evaluated in phase III trials. A study of docetaxel with or without vandetanib showed a PFS benefit, whereas there was no significant difference in PFS with pemetrexed [23, 24]. Recent trials utilizing sorafenib on the backbone of cisplatin/gemcitabine or carboplatin/paclitaxel for stage IIIIB/IV lung cancer, showed no difference in OS [25, 26]. Similarly, motesanib did not significantly improve survival [27]. It is likely that randomized trials of anti-angiogenic agents will require predictive biomarkers in order to refine their optimal population; biomarkers might include VEGF, or a genetic alteration of the receptor/ligand or other genomic/proteomic alteration [28].

Should older patients be treated with bevacizumab? In this meta-analysis, diminished activity of bevacizumab in older patients was not seen, while the single-trial sub-analysis of ECOG 4599 suggested no benefit for older patients. Of interest, Zhu et al. recently evaluated the survival effect of bevacizumab when added to carboplatin, paclitaxel utilizing a large Medicare database and failed to show a survival difference between patients treated with the triplet regimen compared with patients treated with the doublet during similar time frames [29]. However, this was not a randomized comparison and therefore, is subject to bias. Nevertheless, it suggests that the addition of bevacizumab to paclitaxel-based doublet chemotherapy since its approval in the United States has not led to improved survival data in this Medicare population.

In summary, the meta-analysis provided here may not allow us to truly improve our assessment of the role of bevacizumab in combination with chemotherapy for advanced-stage NSCLC. Its precise contribution to increasing survival remains unclear. ECOG–4599 will continue to dominate current treatment recommendations and the only evidence-based regimen to which bevacizumab should reasonably be added as a standard remains carboplatin and paclitaxel. The addition of bevacizumab to pemetrexed remains of some interest. However, until data provide evidence to the contrary it can be hypothesized that a pemetrexed-based doublet would be equivalent to the carboplatin, paclitaxel, bevacizumab triplet [1, 15]. In that case, the doublet would likely be more tolerable and cost-effective. In case the triplet pemetrexed-based treatment was shown to be superior to its doublet, the ‘Pointbreak’ trial shows the paclitaxel triplet combination to be similarly active and it would likely remain the standard in clinical practice, again based on the cost-effectiveness. Finally, predictive markers are needed. Anti-angiogenic therapy continues to hold promise and clearly benefits some patients. Given the associated cost and toxicity however, optimizing the patient-population exposed to these agents remains a high priority.

disclosure

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references

Whole-body 18FDG–PET/CT or whole-body gadolinium-enhanced MRI for distant staging?

The goal of cancer imaging is an extensive and comprehensive assessment of the disease to tailor treatment to an individual patient and to offer a reference ‘baseline study’ for future therapy response assessment. In some cases, whole-body (WB) examination is needed and different techniques have been developed to address WB imaging. WB contrast-enhanced CT has been widely used in this setting but 18F-fluorodeoxyglucose positron emission tomography (18FDG–PET), and more recently, 18FDG–PET/CT, have become important tools. Also, for a number of situations in oncology, 18FDG–PET/CT is the standard of reference modality. In France, ~200000 examinations with 18FDG–PET/CT are carried out per year. PET/CT is usually carried out from skull base to mid-thigh level but can be easily switched to WB without any instrumental modification. Since the introduction of newer software and hardware developments, MRI also has WB imaging capabilities with unique advantages and drawbacks. Last but not least, diffusion-weighted imaging (DWI) is available for WB-MRI and is seriously challenging 18FDG–PET/CT in different settings.

Given this panorama, there is the need to compare these different tools. The meta-analysis by Xu et al. [1], in the current issue of the journal, aims to assess the available studies that compared gadolinium-enhanced WB MRI with WB 18FDG–PET/CT. Not many pooled analyses on this topic exist, and the information provided is therefore of interest. WB MRI included nonenhanced T1, T2 and contrast-enhanced T1 sequences and most studies also used a short-time inversion recovery (STIR) sequence. DWI was not used or not considered. The CT part of PET/CT was carried out with or without contrast enhancement (CE).

In their meta-analysis, Xu et al. included 13 studies (1239 patients). For the nine studies providing information per patient, average sensitivity and specificity resulted almost equivalent for WB-MRI (Se = 85%; Sp = 97%) and 18FDG–PET/CT (85%; 96%). Analysis per lesion in four studies also resulted in almost similar sensitivity and specificity (WB-MRI: 88%; 89% and 18FDG–PET/CT: 85%; 90%). While this information on a global similar performance of the two imaging modalities is of interest, there are a number of points that require clarification to understand the impact of these results in clinical practice:

- Because the number of available studies is small, the meta-analysis includes studies of various tumor types (four on pharyngeal carcinoma from a single institution, three on non-small-cell lung cancer, two on melanoma, one on breast cancer and one on colorectal cancer, as well as two pilot studies mixing various tumor types). Also, no subgroup analysis for tumor types could be offered. However, different tumor types might not be comparable. As regards PET/CT, 18FDG avidity can be quite different from one tumor type to another. Some tumor types would not be good candidates for PET/CT examination because of low 18FDG avidity; hormone-dependent prostate cancer is a notable example.
- Clinical settings are also heterogeneous, combining studies of primary staging and others of restaging. When reading the available literature evidence on the topic of WB imaging