Editorial

Another disappointing result, but how good is it?

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Neoangiogenesis is one of the major hallmarks of cancer (1). New vessels are constantly growing from existing cells and provide nutrients and oxygen to cancer cells. Vascular endothelial growth factor (VEGF) is the main inducer of angiogenesis. VEGF binds mainly to VEGF-receptor 2 (VEGFR-2). Targeting this signal in combination with traditional cytotoxic chemotherapy is a reasonable strategy. This should block one of the major factors affecting cancer growth without causing overlapping toxicity. Two agents already show clinical efficacy in this regard and have been approved. The first was bevacizumab, a humanized monoclonal antibody directed against VEGFR. This was followed by ramucirumab, a human immunoglobulin G1 monoclonal antibody targeting VEGFR-2.

The efficacy of bevacizumab has been validated in many cancers and it has been approved by the Food and Drug Administration for use in cervical cancer, colorectal cancer, glioblastoma, non-squamous non-small cell lung cancer (NSCLC), ovarian and fallopian tube cancer, primary peritoneal cancer, and renal cell cancer. Off label, it has been used in breast cancer, endometrial cancer, malignant pleural mesothelioma, soft tissue sarcoma, and angiosarcoma. The Italian clinical trial group (Gruppo Oncologico Italiano di Ricerca Clinica) verified the efficacy of bevacizumab in patients with extensive small-cell lung cancer (SCLC) in combination with cisplatin and etoposide. Cisplatin and etoposide has been the standard treatment of SCLC for more than 30 years (2). The development of chemotherapy for SCLC has fallen behind that of other lung cancers. No targeted therapy or immunological agent has been shown to be effective. Only a Japanese study reported that irinotecan was superior to etoposide in combination with cisplatin (3), although this result was not reproduced in another study (4).

Increased toxicity is a major concern when adding bevacizumab to chemotherapy. In NSCLC, severe hemoptysis was seen in 6 of 66 patients who had major bleeding in a phase II study and 4 of these had squamous histology (4). Therefore, a further development was the discovery that bevacizumab helped patients with non-squamous histology. Patient selection based on histology was a pioneering concept, which has since become the standard algorithm in NSCLC. However, histology is not the only risk factor for hemoptysis. Tumors in the hilar region and those invading major vessels are also concerns. Indeed, in a subsequent study that excluded patients with squamous cancer, 1.9% of the patients had major bleeding (5). SCLC generally has massive tumors in the mediastinum and these have a high risk of hemoptysis. However, in the study that evaluated bevacizumab in SCLC, no patient had grade 3 or worse hemorrhage, even in the bevacizumab group (2). Furthermore, only manageable hypertension was increased more frequently in the bevacizumab arm. These results show that the study successfully identified patients suitable for bevacizumab therapy in terms of toxicity.

One impact of the study was another negative result in SCLC. The hazard ratio (HR) (95% CI) of progression-free survival (PFS) was 0.72 (0.54–0.97) and the overall survival (OS) was 0.78 (0.5–1.06). Statistically, patients in

the cisplatin and etoposide arm should have had a median survival of 9 months and a 1-year survival of 40%. However, the median OS in the cisplatin and etoposide arm was 8.4 months and the 1-year survival was 25%, which were lower than expected. Only the secondary end point of PFS was significant, while the primary end point, i.e., the OS, did not reach the estimated efficacy. This characteristic of prolonging PFS, but not affecting OS, is the major pattern of failure in bevacizumab treatment. It has been reproduced in metastatic breast cancer in combination with paclitaxel, in prostate cancer in combination docetaxel and prednisolone, and in metastatic NSCLC in combination with cisplatin and gemcitabine (6-8). It remains unclear whether PFS is a suitable surrogate marker for advanced cancer (9,10). The studies that show a statistical difference in PFS but not in OS support the idea of the disadvantage of PFS. Generally, the difference in OS is smaller than that in PFS (11). In this study, the HR of the PFS and OS was 0.72 and 0.78, respectively, and did not differ much. This could be due to the lack of effective treatment after the up-front platinum doublet chemotherapy in SCLC. Regardless, bevacizumab did not prolong the OS of SCLC patients in this study.

A statistical difference does not equal a clinical difference. The golden rule for a clinical trial is to set a meaningful clinical difference and frame the study to validate it. Since clinical value may refer to survival, toxicity, cost, and other parameters, it is frequently interpreted broadly. For example, when the toxicity of the new agent is preferable to that of the standard treatment, but the study design was inferior, how much of a difference in survival is permissible? Even for an agent with similar toxicity and a superior study design, how large should the difference in OS be for it to be approved?

There are no definite consensus-built answers to these questions; however, many researchers are examining this issue. The American Society of Clinical Oncology is developing a framework (12) and introducing the concept of meaningful outcomes to clinical trials (13). Recommended targets are declared for each cancer. For example, in squamous cell lung cancer, the current baseline OS is set to 10 months and the targeted improvement in OS is 2.5–3 months with a HR of 0.77–0.8. If we extrapolate this target to SCLC, it is conceivable to consider that the HR of 0.78 in this study is sufficient for bevacizumab to be evaluated as effective. Therefore, the major reason that this study failed to demonstrate its efficacy was the expectation of an extreme improvement in survival. The 1-year survival was hypothesized to improve by 18%. In fact, the point estimation of the HR in the study that added bevacizumab to carboplatin and paclitaxel in non-squamous NSLC was 0.79. Note that this study was funded by the government, and the funder asked that this difference be shown in the evaluation of bevacizumab. Therefore, bevacizumab in SCLC may be as effective as it is in NSCLC, but not sufficiently effective for the government, who pay for the drug.

A clinical trial is the scientific method used to evaluate treatment. It is the basis of most oncology practice and is required for the approval and re-imbursement of an agent. Since the costs of drugs are increasing dramatically, all of the stakeholders in medicine, including patients, providers, payers, and the industry, are affected by this issue (14). Limiting the cost of a clinical trial so that it shows only a sufficient difference may be a solution. Compromises between scientific and economic issues are becoming increasingly visible. Finding biomarkers to identify more appropriate patients for anti-angiogenic therapy is warranted.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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