

Thalidomide in Small Cell Lung Cancer: Wrong Drug or Wrong Disease?

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Small cell lung cancer (SCLC) accounts for about 15%–20% of lung cancers, and two-thirds of SCLCs are diagnosed as extensive disease. SCLC is very sensitive to chemotherapy, with initial response rates varying between 70% and 85%. Current standard chemotherapy consists of a combination of a platinum compound with etoposide. Thoracic radiotherapy is recommended in limited disease, as well as prophylactic cranial irradiation in chemotherapy-responding patients, allowing a modest gain in overall survival. However, the vast majority of patients rapidly relapse, develop resistance to therapy, and present an aggressive clinical course. No major therapeutic progress has been achieved in SCLC in the past decade and prognosis remains dismal, with about 11% and 2% survival at 5 years in limited disease and extensive disease, respectively (1).

Anti-angiogenic therapy is emerging as a new approach in cancer treatment. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, provides progression-free survival benefits when combined with interferon alpha in metastatic renal cancer and in combination with chemotherapy in advanced breast cancer, as well as a survival benefit in colorectal and non-small cell lung cancers, in combination with chemotherapy. VEGF receptor tyrosine kinase inhibitors also prolong survival in renal and hepatic carcinoma (2). Tumor angiogenesis is expected to play a role in SCLC because VEGF is expressed in approximately 80% of the cancers (3).

In this issue of the Journal, Lee et al. (4) reported the results of a randomized, double-blind, placebo-controlled trial in SCLC combining thalidomide, a drug with bona fide anti-angiogenic activity, with carboplatin and etoposide chemotherapy. The study is sound and the results are without appeal—thalidomide combined with chemotherapy does not extend progression-free or overall survival compared with chemotherapy alone. Worse decreased survival of patients with extensive disease, and increased risk of thrombotic events were observed in thalidomide-treated patients.

In 2008, Pujol et al. (5) already reported a phase III study in which thalidomide was added to etoposide, cisplatin, cyclophosphamide, and 4-epidoxorubicin-based chemotherapy to extensive disease patients who initially responded to two cycles of chemotherapy. No survival benefit compared with chemotherapy alone was observed. Previously, two small phase II studies testing thalidomide with carboplatin–etoposide followed by a thalidomide maintenance in patients with extensive disease suggested evidence for activity (6,7), and another phase II study, using an irinotecan–carboplatin regimen, did not (8). Treatment-related side effects (including neuropathy, emesis, constipation, drowsiness, neutropenia, thrombotic events) led to thalidomide discontinuation in several patients included in these trials (5,8). Nowadays, the phase III studies by Pujol et al. and Lee et al. definitely close the door to using thalido-

midomide in SCLC (9). These negative studies, however, must not be disregarded. Rather they should provoke a discussion on why thalidomide failed in SCLC and where to go from there.

Two simple explanations addressing these failures can be advanced at this time to launch the discussion. Either something is wrong with thalidomide itself or SCLC could be the wrong cancer to test it.

To the first explanation: Thalidomide might not be an effective anti-angiogenic drug as initially assumed. Although thalidomide was shown to suppress angiogenesis 15 years ago, the responsible mechanism has remained largely elusive (10,11). Its main biological activities appear to be inhibition of inflammation (eg, suppression of nuclear factor kappa-B, cyclooxygenase-2, tumor necrosis factor, interleukin-1 and -6) and immunomodulation (eg, stimulation of T-cell activity and T helper cell 1 differentiation) (11). In humans, although thalidomide was reported to modulate the expression of angiogenic molecules (12), there is no direct evidence that its therapeutic efficacy in multiple myeloma and erythema nodosum leprae (the two indications for which thalidomide has been recently registered after its withdrawal in the 1960s because of its teratogenicity) is due to the inhibition of angiogenesis (13). Considering the role of myeloid and inflammatory cells in promoting angiogenesis (14), one could contemplate the possibility that the supposed anti-angiogenic effect of thalidomide is secondary to its anti-inflammatory activity and thus be context dependent. Because SCLC is poorly infiltrated with inflammatory and immune cells, thalidomide may simply miss the target. Unfortunately, from these studies, we will not know whether thalidomide modified angiogenesis in treated patients. This condition reminds us that we deeply need validated biomarkers of angiogenesis to monitor anti-angiogenic effects in patients (15).

To the second explanation: SCLC might be the wrong disease to test thalidomide and possibly other anti-angiogenic drugs.

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Clearly, not every tumor is equally angiogenic or equally dependent on angiogenesis. The extreme example is renal cancer, which presents a strong activation of the VEGF pathway, is highly angiogenic, strongly depends on angiogenesis, and responds well to the VEGF inhibitor bevacizumab and to the VEGF receptor tyrosine kinase inhibitors sorafenib and sunitinib (16). By contrast, some tumors may grow by using preexisting vessels (vascular co-option) or by forming vessels through intussusception (17). Furthermore, tumors can rapidly adapt to inhibition of angiogenesis and develop resistance (18). Unfortunately, at this point, we still know little about the vascular biology of SCLC, its dependence on angiogenesis, and its mechanisms of adaptation to anti-angiogenesis to predict whether SCLC is possibly sensitive to angiogenesis inhibition.

Where do we go from there? Concerning thalidomide, the notion that this drug has clinically significant anti-angiogenic activity should be revisited. In future studies, if any, it will be important to collect direct evidence for anti-angiogenic effects in treated patients by using biomarkers of angiogenesis, in particular imaging-based approaches (15). Furthermore, in view of its anti-inflammatory and immunomodulatory effects, and the angiogenesis-promoting effects of inflammation, solid cancers with a strong inflammatory component, such as melanoma and colorectal, liver, prostate, and some breast cancers, should be preferred (19). Concerning anti-angiogenesis in SCLC, before any new anti-angiogenic therapy is tested, it is reasonable to await the outcome of the 13 ongoing trials investigating bevacizumab in various combinations. Two bevacizumab-based phase II trials were reported in 2007, one of them suggesting a potential improvement of progression-free survival, with acceptable toxicity, however not compelling enough to progress to a phase III trial (20,21). A randomized phase II trial using the VEGF receptor tyrosine kinase inhibitor vandetanib in maintenance therapy after standard chemotherapy and radiotherapy in limited disease and extensive disease could not demonstrate any progression-free or overall survival benefit (21).

In conclusion, developing novel anti-angiogenic drugs and therapies remains a major challenge in clinical oncology, and in this regard, SCLC is a particularly difficult case because its biology is still not fully characterized. Insufficient knowledge of its biology may have also contributed to the systematic failure of targeted therapy approaches attempted (22). Rather than running from failure to failure, it may be more reasonable to go back to experimental work, including the development and analysis of transgenic SCLC models (23), to better understand SCLC biology and identify robust therapeutic targets. Concerning phase I and II trials with anti-angiogenic compounds, the measurement of functional, cellular, or molecular parameters of angiogenesis may provide evidence on drug activity and tumor–host response that clinicians can use to determine whether or not move on to large and costly phase III trials (15).

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Note

C. Ruegg holds stock in Diagnoplex, a company dedicated to discover and optimize combinations of molecular biomarkers to detect cancers at an early stage and receives research funds from Novartis to test the effects of bisphosphonate (Zoledronate) on tumor angiogenesis.