Reply to the letter to the editor ‘Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC’ by Ou et al.

We agree with the thoughtful comments and insightful questions raised by Drs Leduc and Besse which indeed we hope our article will engender. The limitations of this retrospective analysis has been acknowledged in the discussion section of our article [1] and again summarized by Drs Leduc and Besse. Despite these limitations, we did identify performance status at the time of progressive disease (PD), prior response to crizotinib (complete/partial response versus stable disease), and the appearance of new lesion or not are important prognostic factors in determining progression-free survival outcome in addition to the ability to continue of crizotinib beyond PD in a multivariate analysis. The limitations of the current RECIST criteria especially as they are applied to defining PD in tyrosine kinase inhibitor (TKI)-driven therapy have been discussed in details [2]. PROFILE 1001 was initiated in 2007 and PROFILE 1005 was initiated in 2009 at a time when the management of NSCLC driven by actionable driver mutations was less sophisticated. The fact that both trials allowed continuation of crizotinib treatment beyond RECIST progression without regards to the site of disease progression, performance status, or the types of locoablative therapies as long as the clinical investigators deemed the patients are deriving clinical benefit allowed us to better understand the natural history of ALK-rearranged NSCLC at a time when this information was limited. It is also a testament to the already sophisticated understanding of the management of NSCLC with actionable driver mutations among the investigators that 62% of the patients were continued on crizotinib beyond disease progression. Our article also lends support that many ALK-rearranged NSCLC patients will benefit uninterrupted ALK inhibition even at PD as disease flare have been reported in literature [3, 4] and likely experienced by many clinicians although its true incidence and predictability is unknown as mentioned by Drs Leduc and Besse. We were not able to capture the true incidence of disease flare but 80% of the 74 patients who did not continue crizotinib beyond PD died <3 weeks of PD as described in our article [1]. In order to fully answer the question posed by Drs Leduc and Besse short of a randomized clinical trial, knowledge of the total tumor burden, site(s) of disease progression, resistance mechanisms to crizotinib [5, 6] and even the actual ALK fusion variants [7] will be needed to help guide decision making as to (i) the optimal time to switch and (ii) which particular second-generation ALK inhibitor to switch to.

S.-H. I. Ou1* & J. Pasi2

1Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center, Orange

2Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA

(*E-mail: siou@uci.edu)

disclosure

The authors have declared no conflicts of interest.

references


doi: 10.1093/annonc/mdu258

Published online 17 July 2014

Erlotinib treatment of meningeal carcinomatosis in lung cancer: more is better

A considerable number of patients with lung cancer develop leptomeningeal metastases (LM), associated with poor survival. Several series of patients with epidermal growth factor receptor (EGFR)-mutated lung adenocarcinomas have described weekly, high doses of erlotinib as an effective treatment of LM [1, 2], based on the hypothesis that higher concentrations in the cerebrospinal fluid can be reached by higher systemic concentrations. Our study illustrates the pharmacological limitation of the weekly schedule and presents the case of a patient undergoing a biweekly, high dose of erlotinib.

A 60-year-old, nonsmoking woman developed cephalgia and neck stiffness. She had a 14-month history of stage IV lung adenocarcinoma harboring an activating mutation of the EGFR due to the deletion of five amino-acids on exon 19. She had previously received 150 mg/day erlotinib, with initial clinical benefit, however no sustained response and lung tumor progression after 6 months. She then received pemetrexed, platinum and bevacizumab with a complete lung response for 10 months. Magnetic resonance imaging (MRI) showed a right inferior colliculus and LM. Systemic chemotherapy was interrupted due to meningeal disease progression and a weekly high dose (1500 mg) of erlotinib...
was initiated, as previously reported [1]. Neurological symptoms disappeared for 2 days, before reappearing. The trough plasma erlotinib level was 224 ng/ml at day 7 after erlotinib intake. Utilizing a biweekly schedule, a rapid and sustained complete neurological remission was observed and maintained for 6 months. Grade 2 rash and diarrhea were the worse toxicities. Mean trough plasma erlotinib level before each intake was 439 ng/ml (n = 12; range 251–761). Pulmonary disease progression occurred and reintroduction of chemotherapy was concomitantly required to control both meningeal and extrameningeal disease.

Recently, Kuiper et al. showed that a weekly, high dose of erlotinib is not effective in patients with acquired extracranial disease treated with a standard dose of erlotinib [3]. The higher plasma peak of erlotinib obtained with the biweekly schedule probably generated therapeutic concentrations in CSF. Although the biweekly schedule did not generate the suggested trough plasma therapeutic range (848–1684 ng/ml) for the control of pulmonary disease [4], our case illustrates that a biweekly, high dose of erlotinib could be a feasible regimen to achieve rapid and sustained meningeal disease control. Ethical considerations were central in the decision-making process. We suggest that physicians should consider LM as a distinct entity, thus being ready to reinforce its treatment and be open to combine concomitant specific treatments for both LM and extrameningeal disease.

A. Cessot*, B. Blanchet2 & F. Goldwasser1

Departments of 1Medical Oncology, Université Paris Descartes; 2Pharmacology, Cochin Teaching Hospital, Paris, France
(*E-mail: anatole.cessot@cch.aphp.fr)

**disclosure**

The authors have declared no conflicts of interest.

**references**


doi: 10.1093/annonc/mdu261
Published online 23 July 2014

**Treating breast cancer with trabectedin: a new arsenal**

Trabectedin is a novel marine-derived alkaloid agent that specifically targets DNA nucleotide excision repair machinery. Although, it is not yet commercially available in the United States (but approved in Europe), it is an active agent for several subtypes of soft tissue sarcomas including myxoid/round cell liposarcoma and leiomyosarcoma [1]. In *Annals of Oncology*, Delaloge et al. [2] reported results of a single-arm study of 40 patients with metastatic breast cancer (MBC). Patients entering the study had to have previously treated MBC with germline BRCA1 or BRCA2 mutation. Treatment with trabectedin yielded a confirmed partial response rate of 17% and median progression-free survival (PFS) of 3.9 months. In addition, many heavily pretreated patients demonstrated reduction in target lesions on imaging studies. Delaloge et al. interpreted their data positively, concluding that treatment with trabectedin is safe and warrants further evaluation in MBC.

We believe that the findings of this nonrandomized, open-label, multi-institutional, phase II trial are encouraging but should be interpreted with caution because of several reasons. The study population had a median of four prior lines of treatment; predominantly composed of patients with breast cancer of ductal subtype, BRCA1 mutation and without hormone receptors expression. The primary end point of this trial was to determine response rates rather than PFS. In addition, because this study was small with only 35 assessable women and because it had no control group, it would be impossible to draw any definitive conclusions about the effectiveness of the therapy. This trial was closed due to the low recruitment rate. The cause of poor accrual has not been explained, although this study was an international collaborative effort. The response rates and median PFS in this study are quite similar to previously reported data in this patient population [3]. It is not clear why trabectedin was given at a dose of 1.3 mg/m2 in this study when the recommended and approved dose of this agent is 1.5 mg/m2 [4]. The rationale and number of patients who received granulocyte colony-stimulating factor (primary/secondary prophylaxis) has not been explained. The proportion of patients with CPK elevation (26%) is much higher than previously observed with this agent in MBC [5]. It seems that the study protocol was not exactly followed as 7.5% patients without target lesion were enrolled, although the study protocol required measurable disease per RECIST criteria for eligibility. Finally, the findings of this study of relatively young and fit patients may not apply to most patients with MBC seen in clinical practice.

On the basis of an increase in response rate, Delaloge et al. imply that trabectedin is an advance in the treatment of MBC. Although, response rates are often used for active new agents in phase II studies, this efficacy measure is an unreliable indicator of benefit in MBC. A positive correlation between response rates or PFS and overall survival or quality of life in MBC is currently lacking. Nevertheless, these results are a positive step forward but further evaluation is needed to elucidate the value of this agent in MBC. The courageous breast cancer women who volunteer for these studies deserve nothing less.

L. Malik*

Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, USA
(*E-mail: malikl@uthscsa.edu)