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 chemotheraphy 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.

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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.

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Reply to the letter to the editor ‘Treating breast cancer with trabectedin: a new arsenal’ by L. Malik

We are grateful to Dr Malik for his interesting comments and agree that the findings of this phase II trial are encouraging. Indeed, trabectedin’s efficacy has been repeatedly suggested, through in vitro and in vivo findings, to be related to homologous recombination (HR) repair abnormalities involving ERCC1/X and BRCA1 [1, 2]. This study was the first to target such a BRCA1/2-mutated population with an HR-directed agent. Certainly, due to the limited patient population, trabectedin activity observed in BRCA-mutated metastatic breast cancer patients should be considered with caution; as clearly mentioned in the study publication.

However, we believe the results of the trial are positive and worthy to be disseminated. The study population consisted of highly pretreated patients (median of 4, but up to 10, previous therapy lines in the metastatic setting), all carrying BRCA1/2 germline mutation, of whom 52.5% had triple-negative breast cancer. Tumor response rate (RR) by RECIST was chosen as primary end point to have a proof of concept of trabectedin activity in this rare population, as well as to have a dichotomous variable to perform a futility analysis. Progression-free survival (PFS) was a prospectively defined secondary end point. Both were assessed by an independent review board.

As per protocol, only treated patients with measurable disease were assessable for efficacy. Therefore, of the 40 recruited patients, 2 received no study treatment and 3 did not have target lesions by independent radiological review (although they did by investigator assessment). Consequently, and as indicated in the publication, the remaining 35 were assessable for efficacy. Although the approved dose for single-agent trabectedin in sarcoma is 1.5 mg/m² as a 24-h infusion every 3 weeks, the dose used in this trial (1.3 mg/m² as 3-h infusion every 3 weeks) appeared to be similarly active in prior trials with other indications [3] and more convenient for the patients and is widely used in practice. Also per protocol, granulocyte colony-stimulating factor was not allowed as primary prophylaxis; nine patients (22.5%) received it as secondary prophylaxis, according to the investigators’ criteria.

The safety profile was acceptable, with no cumulative toxicities. Creatine phosphokinase (CPK) elevation, which occurred in 26% of the patients, was reversible and similar to that observed in the pool of phase II trials with trabectedin monotherapy (23.2%) [4]. None of these episodes of CPK elevation had clinical manifestations. This parameter was not recorded in the study mentioned by Dr Malik for the comparison of CPK increase incidences [5].

The very low recruitment rate (40 patients in 4 years), was due to the rarity of already identified BRCA1/2-mutated breast cancer patients with metastatic disease; at that time, BRCA1/2 testing criteria were much narrower than at the present time.

Overall, we agree with Dr Malik that, in this heavily pretreated population that still has an urgent and unmet medical need, a RR of 17% and a PFS of 3.9 months together with an acceptable benefit/risk ratio represent a step forward and deserve further evaluation.

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