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Editorial

Sunitinib in breast cancer: Friend or foe

The paper by Liljegren et al. published in this issue of The Breast has created a lot of controversy among the members of the Editorial Board and reviewers of the manuscript. We eventually decided to publish it despite the fact that is describes selective clinical cases treated within the scope of a larger, prospective clinical trial. The main argument for publication is to provide clinical insight regarding the main toxicities and routine management of patients treated with this new antiangiogenic agent. Any consideration regarding the potential promising anticancer activity of the combination docetaxel and sunitinib should be reserved for the presentation and publication of the full results of the clinical trial and cannot be inferred from this manuscript.

The concept of using VEGF tyrosine kinase inhibitors to treat metastatic breast cancer (MBC) is attractive since there is a strong scientific rationale, facility of oral administration, and the existence of some solid data regarding the efficacy of antiangiogenic therapies in breast cancer such as bevacizumab or, indirectly, metronomic chemotherapy.

The available data on sunitinib activity and tolerability in MBC are discussed comprehensively in the paper by Liljegren et al. Sunitinib, in particular in combination with chemotherapy, is considered by many a toxic agent with a negative impact on patients' quality of life, in spite of significant antitumor activity. The paper by Liljegren et al provides evidence that, in the hand of experienced investigators and with the correct supportive measures, sunitinib's toxicity profile is not only manageable but can even be associated with an improved quality of life. Additionally and of crucial importance, the toxicity profile of this new agent is clearly dependent on the dose and schedule used.

There are scarce published data on the use of sunitinib in breast cancer.[2] In the only fully published study, in heavily pretreated MBC patients sunitinib monotherapy (given 50 mg/day on a schedule 4 weeks on/2 weeks off), demonstrated promising antitumor activity at the cost of non-negligible but manageable toxicity. The most frequently reported adverse events (AE) were fatigue, nausea, diarrhoea, mucosal inflammation, and anorexia. Grade 3 AE reported in five or more patients included fatigue and hand-and-foot syndrome. Additionally, 5% of patients demonstrated grade 4 laboratory abnormalities: hyperuricemia, increased liver function tests and neutropenia. More than half of patients on sunitinib monotherapy required dose interruption and almost 40% of patients needed dose reduction.[2–4] When given in combination with taxanes, the most commonly observed complication was severe neutropenia. Other adverse events included grade 3 fatigue, diarrhoea, hand-and-foot syndrome and neuropathy.[3,4]

In the paper by Liljegren et al, MBC patients received docetaxel (75 mg/m2) on day 1 of each 3-week cycle followed by sunitinib (37.5 mg/day for 2 weeks followed by 1 week off treatment [Schedule 2/1]). The main toxicities observed were typically related to docetaxel treatment (febrile neutropenia, peripheral neuropathy, myalgia/arthralgia, fluid retention, nail changes), but a significant number of adverse effects, such as fatigue, rash and gastrointestinal symptoms, were most likely related to sunitinib. All these side effects were manageable, did not require treatment withhold and rarely required dose reductions; one could therefore anticipate that, if this toxicity profile is confirmed in the full trial, it will allow for the routine use of the docetaxel–sunitinib combination, should a favourable antitumor activity be demonstrated in large phase III studies.

The main message from the paper by Liljegren et al and from this commentary is that, even in the era of targeted therapy, all efforts should be made to understand correctly and as early as possible in the process of drug development, the optimal way to deliver a new agent. This optimal way is usually a compromise between maximizing antitumor activity and minimizing adverse events. Only a deep knowledge of potential side effects, judicious use of supportive and occasionally preventive measures, optimal dose and schedule of administration, will allow us to make the best of these promising new drugs that albeit "targeted" are not deprived of side effects.

Sunitinib is currently being extensively studied in breast cancer – the search on ClinicalTrials.gov reveals 28 ongoing trials (at different stages of conduct) of this compound used alone or in combination with several other agents; five of these 28 trials are testing the combination of sunitinib with docetaxel.[1] The results of these trials will hopefully allow to clearly define the role of this compound and this association in breast cancer.

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