

## LETTERS TO THE EDITOR

### Problems in dealing with very rare adverse effects of new anticancer drugs: the example of trabectedin

**To the Editor:** The paper by Stoyianni *et al.*<sup>1</sup> reports a case of rhabdomyolysis in a uterine leiomyosarcoma patient treated with three cycles of trabectedin after failure of two previous chemotherapy lines (doxorubicin-ifosfamide and gemcitabine-docetaxel). Liver tests before the third cycle of trabectedin were within the normal range, except for a modest increase in alkaline phosphatase, which was 20% higher the upper normal limits. After the third cycle, the patient exhibited a marked elevation of serum creatine phosphokinase, achieving the maximum value at day 14 and then gradually declining with a clinical improvement and a full biochemical and clinical recovery on day 43. As noted by the authors, the patient received several other drugs such as carvedilol, ramipril, glyceryl trinitrate, digoxin, atorvastatin and enoxaparin concomitantly with trabectedin. Therefore, it cannot be ruled out that the toxicity was due to the treatment with the statin atorvastatin, for which rhabdomyolysis is a possible adverse reaction, or was enhanced by some still not well-defined drug interaction. For example, as discussed by the authors, the concomitant administration of the beta blocker carvedilol might have decreased hepatic clearance of trabectedin. This hypothesis is supported by an already reported case of trabectedin-associated rhabdomyolysis in a patient receiving the same beta blocker.

There is no doubt that oncologists should pay more attention to drug interactions, since most cancer patients receive several other drugs due to concomitant diseases, cancer and/or chemotherapy-associated symptoms. This does not apply only to trabectedin but to any new drug that has recently entered clinical practice. As suggested by the authors of the paper, some other cases of rhabdomyolysis associated to trabectedin treatment – reported in the literature – were clearly related to protocol violations, related to wrong drug doses or patients' ineligibility, i.e., patients with abnormal liver function or a poor performance status.

Generally, case reports do not allow to draw any conclusion on the clinical relevance of a rare adverse reaction possibly associated to a specific treatment and on

the mechanisms behind the observed toxicity. Nevertheless, they can point out a potentially important problem, requiring epidemiological and pharmacological studies on large cohorts of patients. Trabectedin was approved in Europe for second-line therapy of soft tissue sarcomas in 2007 and in combination with liposomal pegylated doxorubicin as second-line therapy for ovarian cancer patients relapsing 6 months after first-line therapy in 2009. Therefore, the number of cases with soft tissue sarcoma or ovarian cancer treated with the drug should be large enough to allow the evaluation of drug-induced adverse reactions. In Italy, 585 soft tissue sarcoma patients have been treated with trabectedin in the last 2 years, and only 3 cases of rhabdomyolysis have been reported. As regards ovarian cancer, 8 cases of rhabdomyolysis have been reported out of a total of 1465 patients included in phase II-III trials. In sarcoma and ovarian cancer patients, the incidence of rhabdomyolysis thus appears to be approximately 0.5%. Generally, when such a low frequency of an adverse reaction of an anticancer drug is reported, prospective investigations aimed at identifying specific risk factors (e.g., genetic polymorphisms of genes coding for drug-metabolizing enzymes, or concomitant treatments) are unlikely to be set up. In the future, as data on many thousands of patients will be available, it will be possible to perform retrospective analyses to generate some testable hypotheses.

In summary, trabectedin-associated rhabdomyolysis, although extremely rare, has certainly to be considered by oncologists as a potential adverse reaction. In most patients, trabectedin, given with dexamethasone premedication, is very well tolerated<sup>2</sup>. However, a careful clinical and biochemical monitoring is mandatory at each cycle, as most cases of severe adverse reactions, including rhabdomyolysis, reported so far are likely to be related to insufficient medical attention, which should be easily avoidable.

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## References

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