Reviewer's report

Title: Herbal-drug interaction induced rhabdomyolysis in a liposarcoma patient: the hidden foe of trabectedin

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Reviewer: Maurizio D’Incalci

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Strippoli et al. reports rhabdomyolysis in a patient with a differentiated liposarcoma receiving trabectedin as second line therapy after antracycline and ifosfamide failure.

The toxicity was observed at the fourth cycle and manifested with G4 pancytopenia with an increase in liver lytic enzymes, serum levels of myoglobin and creatinine phosphokinase and lactate dehydrogenase. The patient took a preparation of chokeberry daily during the last course of trabectedin thus suggesting a possible interaction leading to an increase in the drug toxicity.

There is certainly a growing use of herbal extracts, also in oncological patients and it can be useful to draw the attention of oncologists to the potential risk to assume extracts that interact with pharmacological therapies, thus modifying the activity/toxicity in an unpredictable way.

Therefore to report cases like this is potentially useful.

This referee, however, believes that the title is too emphatic considering that it is a case report:

I suggest as a title:

Herbal-drug interaction induced severe toxicity in a liposarcoma patient receiving trabectedin: a case report highlighting the potential risk of alternative medication given to cancer patients receiving antitumor therapies.

The information related to the chokeberry extract is too limited. Was the extract from leaves?

The authors should specify if it was a commercial preparation and provide details, possibly specifying the compounds that were present in the preparation. From what this referee finds in the literature these extracts generally contain phenolic phytochemicals and especially anthocyanins.

For some of these preparations, if not home-made but produced by a specialized company, it may be possible to obtain information on the amounts of cyanidin-3-galactoside, epicatechin, caffeic acid, quercetin, delphinidin, petunidin, pelargonidin and malvidin etc present in the preparation. Other vitamins and antioxidants can also be present in some preparations in different amounts. Please specify as much as possible.
The authors have correctly pointed out that the metabolic interaction seems to be the most likely mechanism behind the unexpected toxicity. However as many unknown compounds might be present in the preparation it cannot be excluded that other interactions might occur, eg. natural products might share transport mechanisms, activation of death receptors etc.

Perhaps it should be emphasised the multiplicity of potential mechanisms of interaction might apply not only to trabectedin but to many other anticancer drugs that are given in combination.

Many typos were noted: trabectedin was always erroneously written with an i that has to be replaced by an e.

case presentation... man instead men.
the word adriblastin should be replaced by doxorubicin; 0.5-0.7% instead of 0,5-0,7%.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests' below.