Trabectedin: more dangerous than beneficial in ovarian cancer, yet the EMA maintains its position

In the European Union, *trabectedin* (Yondelis®) is an antineoplastic agent authorised for use mainly in recurrent, platinum-sensitive ovarian cancer, in combination with *pegylated liposomal doxorubicin*, an anthracycline. In this setting, addition of *trabectedin* has not been shown to confer any clinical benefit, whereas this drug carries a risk of very frequent and serious gastrointestinal, haematological, hepatic and muscular adverse effects (**a**). Since 2013, *trabectedin* has featured in *Prescrire*'s list of drugs to avoid (1,2).

In 2020, the European Medicines Agency (EMA) reported the premature termination of a clinical trial comparing the *trabectedin* + *pegylated liposomal doxorubicin* combination versus *pegylated liposomal doxorubicin* alone, as third-line treatment in 576 patients with recurrent ovarian cancer. The reasons for this termination were: the absence of any difference in overall survival between the groups; and the increase in serious adverse events reported in the *trabectedin* group (41% versus 21% in the *pegylated liposomal doxorubicin* alone group) with, in addition, an increased incidence of fatal adverse events (3.5% versus 1.8% respectively) and treatment discontinuations due to adverse events (24% versus 11%) (1,3,4).

In mid-2020, the EMA's Committee for Medicinal Products for Human Use (CHMP) nevertheless concluded that the results of this prematurely terminated trial were not sufficiently "*robust*" to call into question the marketing authorisation (MA) for *trabectedin* in ovarian cancer. It compared the profile of the patients in this trial with those included in the trial which led to the MA, and considered that given the differences (number of treatment lines and platinum-resistance), the disastrous results of the terminated trial did not justify reconsideration of the MA (1,3). Yet the trial on which the MA was based did not demonstrate that addition of *trabectedin* provides any clear clinical benefit to patients. As of 2 April 2021, the MA for Yondelis® has not been restricted to women who have received only one line of treatment (1,3).

The CHMP chose not to take into account the data from this trial, even though its results were consistent with the initial evaluation, i.e. showing the significant toxicity of *trabectedin* and the lack of a tangible clinical benefit for patients. Once again, uncertainty has benefitted the pharmaceutical company and has not led, as a first priority, to protecting patients. It is up to healthcare professionals to avoid exposing patients to this drug, which is more dangerous than beneficial.

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***a-** In the European Union, trabectedin is also authorised for use in soft tissue sarcoma, despite an unfavourable harm-benefit balance in this setting (ref 2).*

References **1-** European Commission "SPC-Yondelis" + "Annex IV" 24 September 2020: 25 pages. **2-** "Towards better patient care: drugs to avoid in 2021" *Prescrire Int* 2021; 30 (223): 11 pages (complete review available online). **3-** EMA "Review of Yondelis started" 28 February 2020 + "Authorised uses of cancer medicine Yondelis unchanged following review of new data" 24 September 2020: 5 pages. **4-** EMA - CHMP "Public assessment report for Yondelis. EMEA/H/A-20/1493/C/0773/0060" 23 July 2020: 49 pages.

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