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EDITORIAL

# Lurbinectedin-induced thrombocytopenia: the role of body surface area

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## Abstract

Lurbinectedin is an alkylating agent approved for the second-line treatment of small cell lung cancer. Although initial studies showed no association between body surface area (BSA) and drug clearance, the recommended dose is 3.2 mg/m$^2$ every 3 weeks. This recommendation was based on an exposure–response study, which demonstrated that patients with lower BSA had a higher incidence of thrombocytopenia. Herein we present the factors associated with BSA and thrombopoiesis, which may have contributed to the observed relationship.

**Keywords** Lurbinectedin · Body surface area · Thrombocytopenia · Flat dose · Exposure–response

Lurbinectedin, an alkylating agent, is approved as a second-line treatment of small cell lung cancer (SCLC) at a dose of 3.2 mg/m$^2$ every three weeks [1]. It is hypothesized that lurbinectedin selectively inhibits the oncogenic transcription that binds preferentially to guanines located in the minor groove of DNA and, as a result, adducts and bends the DNA helix towards the major groove, thereby leading to cell cycle arrest and tumor cell apoptosis [2–4]. Lurbinectedin also may affect the tumor microenvironment by modifying the immune-regulatory properties of tumor-associated macrophages, and potentially synergizes with immune checkpoint blockade to generate anticancer immunity [5]. Lurbinectedin is highly protein-bound (99%) to both albumin and α-1-acid glycoprotein. It is primarily metabolized in the liver by CYP3A4 and has a terminal elimination half-life of 51 h [1].

Lurbinectedin received accelerated approval in June 2020, based on a single-arm, open-label phase II trial involving 105 patients with previously treated SCLC, with an overall response rate of 35%. The duration of response was also 6 months or longer in 43% of patients. The dose-limiting toxicity was myelosuppression, including both neutropenia and thrombocytopenia [6]. Interestingly, population pharmacokinetic analyses showed that lurbinectedin pharmacokinetics are not affected by age (18–85 years), body weight (39–154 kg), race, mild or moderate renal impairment, or mild hepatic impairment [7]. This population pharmacokinetic analysis confirmed the findings of the first-in-human trial A-001 regarding the lack of a relationship between clearance and BSA, and as a result, leading to the recommendation to utilize a flat dose of 7 mg for phase II testing [8].

A population pharmacokinetic-pharmacodynamic analysis of 244 patients with advanced solid tumors identified body surface area (BSA) as a covariate affecting the half-maximal effective concentration (EC50) for thrombocytopenia [9]. However, this data set included only 58 male patients (24%), which makes it difficult to discern whether BSA is simply a marker for sex given the obvious differences in body size between men and women or body size (independent of sex) [10]. Given that the vast majority of the female patients had prior myelosuppressive therapy for either breast or ovarian cancer, it is difficult to know whether the findings of this analysis are generalizable to other clinical scenarios.

Most recently, a paper published in this journal by Fernández-Teurel et al. extended the prior population pharmacokinetic and exposure–response (E-R) analyses to include a total of 755 patients, including 99 patients with small cell lung cancer treated at a dose of 3.2 mg/m$^2$ every three weeks in the registration trial [11]. The paper indicates

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that five covariates were analyzed in a logistic regression model for grade ≥ 3 thrombocytopenia: dose, platelets at baseline, albumin, alpha1-acid glycoprotein (AAG), and BSA. Notably, sex was not included as a covariate, although BSA is a reasonable surrogate for sex, which was associated with grade ≥ 3 thrombocytopenia in a multivariate model.

So, is body size (e.g., BSA) or sex the primary determinant of lurbinectedin-induced thrombocytopenia? Firstly, it is well-established that males have significantly higher BSA than females [10]. Although in the adjuvant setting of colorectal cancer, sex was not associated with chemotherapy-induced hematologic toxicity [12], multiple other studies in different settings have shown that female patients are at increased risk of severe hematological toxicity compared to male patients receiving the same treatment [13–18]. A network analysis of platelets obtained from volunteer donors showed that 24 major hubs in pathways associated with megakaryocytic expansion and platelet production were enhanced and activated in males. In contrast, the eleven major hubs in platelets from female donors were either negative or neutral for platelet-associated processes [19]. It is also known that sex hormones affect thrombopoiesis [20]. Therefore, it is crucial to examine the interplay of gender-associated factors such as hormones and subsequent response to chemotherapy-induced thrombocytopenia that may explain the relationship of BSA and thrombocytopenia in the absence of any BSA clearance relationship.

In adults, thrombopoiesis is a 2-stage process entailing the differentiation of hematopoietic stem cells into mature megakaryocytes and releasing platelets from megakaryocytes [21]. The proplatelet formation and release of platelets involve a drastic morphological change in the megakaryocyte, and it is known that expression of ERα and ERβ both were observed in human male and female platelets [22]. This suggests that estrogen could significantly affect the formation and function of platelets [23]. Indeed, a study in mice showed that chronic high physiologic level of estradiol negatively affects platelets production and activation via modulation of platelet proteins such as β1 tubulin [24]. Apart from the effect of estradiol receptors, the presence of the androgen receptor in platelets and megakaryocytes has also been demonstrated, which is associated with a direct effect of testosterone on platelet function [20]. Thus, the effect of sex due to hormonal or other differences could be a lead mediator for the response to chemotherapy-induced thrombocytopenia.

In conclusion, BSA-based lurbinectedin dosing was approved based on a relationship between BSA and toxicity, despite the lack of a relationship between BSA and drug clearance. Further studies are required of this agent (and perhaps others dosed based on BSA) to distinguish the effects of body size and sex on drug-induced myelosuppression. While a dose of 3.2 mg/m$^2$ appears to be safe and effective for the vast majority of patients, it may also be feasible to simply use sex-dependent flat doses (e.g., 5.5 mg for females and 6 mg for males). We are particularly concerned about the risks of unacceptable toxicity in very obese or large patients, since clearance is independent of body size, therefore resulting in very high drug exposure using BSA-based dosing in such patients.

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## Declarations

**Conflict of interest** The authors declare that they have no competing interests.

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