EClinicalMedicine 9 (2019) 5–6

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

EClinicalMedicine
Published by THE LANCET

Commentary

Safely combining trabectedin with radiotherapy to treat myxoid liposarcoma

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ARTICLE INFO

Article history:
Received 26 March 2019
Accepted 26 March 2019
Available online 31 March 2019

Over the past decade, more than 130 novel indications have been approved by the FDA for oncology [1]. These targeted small molecules, biologics, and immunotherapies represent both brand new treatments and novel combination therapies. Radiation therapy is a critical modality used to treat nearly 50% of all cancer patients at some point during their care. Combination drug-radiotherapy holds great promise for patients, yet this potential remains unfulfilled as evidenced by the dearth of combination drug-radiotherapy approvals and the conclusions from a 2018 FDA-AACR-ASTRO workshop focused on clinical development of novel drug-radiotherapy combinations [1]. Because risk of toxicity resulting from combination drug-radiotherapy is of primary relevance to patients, physicians, and regulators, phase I clinical trials for combination therapy must be built on robust scientific rationales. In this issue of EClinicalMedicine, Gronchi and colleagues [2] evaluated the safety and potential synergism of combination trabectedin and radiation therapy in patients with myxoid liposarcoma.

Myxoid liposarcomas are driven by a pathognomonic FUS-DDIT3 translocation and account for 5–10% of adult soft tissue sarcomas, a group of rare, heterogeneous tumors [3]. This study was a first-in-human clinical trial evaluating the safety of combining trabectedin and radiotherapy in localized myxoid liposarcoma. The authors demonstrated that combination trabectedin and radiotherapy had a favorable safety profile at a dose that also exhibited antitumor activity. Previous trials that have evaluated combination chemoradiation in localized soft tissue sarcoma have reported dermatologic, hematologic, and hepatic toxicities [4–6]. It is in this context that the results of the TRASTS trial are promising for trabectedin as an agent in combination drug-radiotherapy.

Potential toxicity of combined chemoradiation is always a concern, especially in cases where therapeutic benefit to patients may be not be significant or uncertain. Thus, although the primary aim of this study was to evaluate safety, any potential synergism between trabectedin and radiotherapy was of great interest. Trabectedin was an interesting compound to combine with radiotherapy in myxoid liposarcoma for several reasons. First, trabectedin is a DNA minor groove alkylating agent that can displace the FUS-DDIT3 fusion protein from its target promoters. Thus, trabectedin has a mechanism of action that may be specific to myxoid liposarcoma cells [7]. Second, trabectedin has been shown to cause cancer cell redistribution to the G2/M phase, which is considered to be more radiosensitive [8]. Third, myxoid liposarcomas are inherently sensitive to radiotherapy [9,10]. These properties may synergize to enhance the response of localized myxoid liposarcoma to radiotherapy. Indeed, pathological and radiological assessments of tumor response to combination trabectedin and radiotherapy from this trial suggest this may be the case.

Combination drug-radiotherapy trials are important for discovering molecules that can synergize with radiation to improve outcomes for cancer patients. If synergy between trabectedin and radiotherapy is demonstrated in the ongoing phase II trial, it opens the door to not only improved local control, but also radiation dose reduction and reduced normal tissue toxicity from radiation. Other ongoing trials such as DOREMY (NCT02106312) are specifically investigating the role of radiation dose reduction in myxoid liposarcoma. The safety profile gained from the TRASTS trial is a critical first step in delivering combination drug-radiotherapies to patients with myxoid liposarcoma. Whether this represents the first step in an advance in clinical practice for myxoid liposarcoma and potentially other soft tissue sarcomas remains to be determined in ongoing and future clinical trials. Furthermore, superiority of combination trabectedin-radiotherapy over either treatment modality alone would be of interest and requires a comparative trial in the future. Similar rational approaches to combination therapy based on mechanistic understanding of radiation and tumor biology has the potential to develop combination drug-radiotherapies to improve outcomes for patients with sarcomas and other cancers in the clinic.

Author contributions

M.C. and D.G.K. wrote the manuscript.

DOI of original article: https://doi.org/10.1016/j.eclinm.2019.03.007.
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https://doi.org/10.1016/j.eclinm.2019.03.015

References

[1] Ahmad SS, Crittenden MR, Tran PT, Kluetz PG, Blumenthal GM, Bulbeck H, et al. Clinical development of novel drug-radiotherapy combinations. Clin Cancer Res 2018. https://doi.org/10.1158/1078-0432.CCR-18-2466.

[2] Gronchi A, Hindi N, Cruz J, Blay J-Y, Lopez-Pousa A, Italiano A, et al. Trabectedin and RAdiotherapy in Soft Tissue Sarcoma (TRASTS): results of a phase I study in myxoid liposarcoma from Spanish (GEIS), Italian (ISG), French (FSG) Sarcoma Groups. EClinicalMedicine 2019;9:37–45.

[3] Antonescu CRLM. Myxoid liposarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. IARC Press; 2013. p. 39–41.

[4] Pisters PWT, Patel SR, Prieto VG, Thall PF, Lewis VO, Feig BW, et al. Phase I trial of preoperative doxorubicin-based concurrent chemoradiation and surgical resection for localized extremity and body wall soft tissue sarcomas. J Clin Orthod 2004;22:3375–80.

[5] Haas RLM, Gelderblom H, Sleijfer S, van Boven HH, Scholten A, Dewit L, et al. A phase I study on the combination of neoadjuvant radiotherapy plus pazopanib in patients with locally advanced soft tissue sarcoma of the extremities. Acta Oncol 2015;54:1195–201.

[6] Jakob J, Simeonova A, Kasper B, Ronellenfitsch U, Rauch G, Wenz F, et al. Combined sunitinib and radiation therapy for preoperative treatment of soft tissue sarcoma: results of a phase I trial of the German interdisciplinary sarcoma group (GISG-03). Radiat Oncol 2016;11:77.

[7] Di Giandomenico S, Frapolli R, Bello E, Uboldi S, Licandro SA, Marchini S, et al. Mode of action of trabectedin in myxoid liposarcomas. Oncogene 2014;33:5201–10.

[8] Simoens C, Korst AEC, De Pooter CMJ, Lambrechts HAJ, Pattyn GGO, Faircloth GT, et al. In vitro interaction between ecteinascidin 743 (ET-743) and radiation, in relation to its cell cycle effects. Br J Cancer 2003;89:2305–11.

[9] Pitson G, Robinson P, Wilke D, Kandel RA, White L, Griffin AM, et al. Radiation response: an additional unique signature of myxoid liposarcoma. Int J Radiat Oncol Biol Phys 2004;60:522–6.

[10] Chung PWM, Deheshi BM, Ferguson PC, Wunder JS, Griffin AM, Catton CN, et al. Radiosensitivity translates into excellent local control in extremity myxoid liposarcoma: a comparison with other soft tissue sarcomas. Cancer 2009;115:3254–61.