T-DM1-related telangiectasias: a potential role in secondary bleeding events

We recently reported five patients who developed diffuse cutaneous telangiectasias [1] with the antibody-drug conjugate T-DM1 (Kadcyla™), combining the cytotoxic activity of emtansine with trastuzumab [2, 3] and which is now EMA and FDA-approved for the treatment of HER2-positive metastatic breast cancer. These observations led us to suggest that bleeding events, which have been reported in 30% of T-DM1-treated patients [2, 3], could be related, at least in part, to induced vascular malformations.

Here, we report five additional cases of metastatic breast cancer patients who developed cutaneous telangiectasias during a phase III study with T-DM1 (3.6 mg/kg i.v. infusion every 3 weeks) (Figure 1A and B). Two of them also presented associated oral mucosal lesions mimicking autosomal dominant hereditary hemorrhagic telangiectasia (or Rendu Osler Weber syndrome) (Figure 1C and D). Moreover, all the patients presented bleeding events of grade 1–3 (primarily epistaxis and gingivorrhagia), despite the absence of thrombocytopenia in three cases or a limited thrombocytopenia of grade 1 in the remaining two other cases. In particular, one patient with diffuse mucocutaneous telangiectasias affecting the tongue, lips and the jugal mucosa (Figure 1C) presented a grade 3 diffuse gastrointestinal hemorrhage with hematemesis and severe anemia. Gastroduodenoscopy evidenced two esophageal-like varices with no associated sign of portal hypertension. Similarly, one patient presented severe bleeding from a cutaneous telangiectasia, requiring the discontinuation of T-DM1. Platelet counts were normal in those last two patients. Finally, we must stress that all patients except one presented with grade 1 elevated transaminases. None of them had other established factors (HIV infection, autoimmune or connective tissue diseases) to explain the appearance of these telangiectasias.

Bleeding events are frequent with T-DM1. They mostly affect the mucosa, manifesting by epistaxis and/or gastrointestinal or gynecologic hemorrhage [2, 3]. So far, they have been attributed to associated thrombocytopenia, which are frequent, with an overall incidence of 32.2% of the cases [2]. The origin of the latter remains unclear but appears mainly linked to the action of T-DM1 on platelet production rather than an alteration of mature platelet function [4]. Nevertheless, those induced thrombocytopenias remain grade 1 or 2 in two thirds of the cases [2]. Moreover, there have been reports of severe hemorrhage in

Figure 1. (A and B) Clinical and histopathological aspect of an induced telangiectasia (in the form of a spider nevus). (C and D) Diffuse oral telangiectasias mimicking a Rendu Osler Weber syndrome.
Withdrawal of hormone replacement therapy might affect multigene signature results in early luminal breast cancer

Clinicians in multidisciplinary teams now use commercially available multigene signatures (MGS) to better distinguish low- from high-risk luminal HER-2-negative breast cancers (BCs). Some health authorities like NICE recommend Oncotype DX to lower adjuvant chemotherapy rates as MGS risk in general, is lower than risk calculations based on patient demographics and tumor characteristics.

Several preanalytical conditions are known to affect MGS results and we claim hormone replacement therapy (HRT) withdrawal may confound MGS results in early BC. A clinical high-risk patient of ours had a high-grade tumor on diagnostic core needle biopsy (CNB), and a lower grade tumor on resection specimen. MGS (PAM50 NanoString Technologies) on CNB showed a luminal B intrinsic subtype and 61 for risk of recurrence score (ROR). The same test on BC from resection specimen 19 days later was luminal A and 24 for ROR. Integration with clinical features classified her in both cases as high risk as lymph nodes were involved. A comprehensive review of the specimens assessed, using standard pathology could not find tumor heterogeneity and showed, apart from a higher mitotic index in CNB an identical morphology in both specimen. The CNB was taken during HRT use while resection was done 13 days after HRT stop.

This observation suggests that a short-term change in hormonal environment before BC surgery might affect MGS results (Figure 1). BC growth and cell proliferation, as measured by Ki-67 expression can change with HRT withdrawal [1]. The fact that MGS in such patients are reported from the resection specimen raises several questions: How to use MGS results in patients on or stopping HRT, respectively, over- or underestimating proliferation? Is this effect of HRT withdrawal on BC cell proliferation similar to aromatase inhibitor use or tamoxifen and long

disclosure

The authors have declared no conflicts of interest.

references


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