Squamous Cell Carcinoma of the Oral Cavity in a Woman With a 9-Year History of Ovarian Cancer: Is Exposure to Pegylated Liposomal Doxorubicin a Factor?

Pegylated liposomal doxorubicin (PLD) is now being used for a variety of cancers and shows a better toxicity profile and, in some instances (e.g., ovarian cancer), more activity than free doxorubicin. Because this improved tolerance allows maintenance use, possible emerging long-term side effects such as secondary neoplasia should be considered carefully.

We are reporting the case of a platinum-sensitive patient (interval free: 29 months) who has developed moderately differentiated squamous cell carcinoma (SCC) of the oral cavity after exposure to PLD. No major risks for SCC were found. There was no history of smoking or alcohol consumption, and the neoplastic tissue was negative for human papillomavirus as well as for p16 expression. The cumulative dose of PLD was 683 mg/m^2, which is considerably lower than those of 11 patients reported in literature [1–6] with doses ranging from 750 mg/m^2 to more than 3,000 mg/m^2, although the latter was administered over a remarkable period of time (5 years).

Briefly, this 65-year-old woman underwent optimal debulking surgery in April 2004 for stage IIIC serous ovarian carcinoma (ER positive, PR positive, MIB1 20%, HER2 90%, grade 2/3, stage IIIC related to abdominal lymph nodes). She underwent adjuvant therapy with eight cycles of paclitaxel-carboplatin and four cycles alternated with the addition of PLD, was enrolled in ICON5 [7] (30 mg/m^2 of PLD every 6 weeks; cumulative dose: 114.4 mg/m^2), and had a negative second-look exploratory reassessment in September 2004. In February 2007, she had a recurrent tumor in the liver that was initially treated with tamoxifen until May 2008, followed by second-line PLD-oxaliplatin until December 2008 (cumulative dose: 508.2 mg/m^2). Oxaliplatin was discontinued after three cycles because of phlebitis.

In February 2009, brain magnetic resonance imaging showed an intra-axial supratentorial mass of secondary origin. The patient underwent radical neurosurgery and then was treated with local brain radiotherapy at 20 Gy (five administrations). Since then, she has done exceptionally well. Cyclophosphamide was given as third-line therapy until July 2010, when a positron emission tomography-computed tomography (PET-CT) scan revealed retroperitoneal lymph node pathological captation confirmed by a further PET-CT scan in January 2012. Lumbo-aortic lymphadenectomy was performed in May 2012. She was treated with letrozole until April 2012, followed by tamoxifen, which was discontinued in November 2012, and lumbo-aortic radiotherapy (45 Gy, 25 administrations). In November 2012, liver recurrence was documented by ultrasonography, and she was again treated with PLD (two cycles; cumulative dose: 60mg/m^2) until December 2012, obtaining partial response. The patient started complaining of an oral cavity lesion, which was initially underestimated by the patient, who used to wear orthodontic braces. The lesion was removed in December 2012, and histological examination showed SCC (pT1pN0pM0, grade 2). Submandibular ultrasonography was negative for lymph node metastases. PLD was discontinued, and the patient is now being treated with gemcitabine-carboplatin with no change in response. In October 2013, another surgical check of same area of the tongue lesion confirmed persistence or local recurrence of grade 2 SCC.

As recently outlined by Muggia [6], it seems reasonable to avoid prolonged exposure to PLD while we await further molecular biology analysis to help identify patients at major risk of developing PLD-related secondary malignancies or the advent of new strategies for reducing these PLD oral effects, such as clinical trials with N-acetylcysteine or other measures for inhibiting potentially carcinogenic activation of "free radicals" from chronic exposure to anthracyclines and their metabolites.

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Disclosures

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