Squamous Cell Carcinomas of the Tongue and Oral Cavity as Secondary Malignancies: What Factors Are Implicated?

FRANCO MUGGIA

New York University Cancer Institute, New York, New York, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

INTRODUCTION

The pegylated liposomal doxorubicin (PLD) was introduced clinically in the 1990s and won FDA approvals for the treatment of Kaposi's sarcoma (1995) and ovarian cancer (2000). Its attenuated toxicities compared with "free" doxorubicin led to strategies of long-term maintenance in Kaposi's sarcoma (KS) [1, 2] and, subsequently, was adopted in our trials for recurrent ovarian cancers. In 2007, the report of Andreopoulou et al. summarized our experience in 16 patients, with seven continuing beyond 4 years without progression of disease; none had stopped the drug because of toxicities, although skin manifestations led to gradually extending treatment intervals up to 8 weeks and some dose reductions [3].

This unique tolerance and "safety profile" continues with regard to absent cardiac or hematologic manifestations. However, in late 2010, we reported [4] two concerns: (1) the development of renal disease in one patient from this original series joined by other instances in a later trial of PLD + bevacizumab [5], and (2) a diagnosis of high-grade dysplasia in one patient, invasive squamous cell carcinomas of the tongue in another, and multifocal tumors of the oral cavity in a third patient. After presenting a poster at the ASCO Annual Meeting 2011, which reported on the development of these cancers [6], we diagnosed two others as reported in the December issue of *The Oncologist* [7]. Three additional reports of squamous cell carcinoma (SCC) as a secondary malignancy in patients receiving PLD for other diagnoses appear as Letters to the Editor in the same issue, and join reports in the recent [8] and older [2] literature that dealt with KS.

Doxorubicin, its analog—epirubicin, and other drugs whose actions involve in part topoisomerase II-mediated DNA cleavage have been previously identified as contributory factors in the development of acute myeloid leukemia and myelodysplastic syndrome following treatment of breast cancer [9], lymphomas [10], and pediatric solid tumors [11, 12]. In particular, anthracyclines have been directly implicated in the translocation t(15;17) of acute promyelocytic leukemia [13, 14]. However, in spite of their mutagenic and carcinogenic properties in defined experimental settings, their clinical use has not been associated with an increase in other secondary neoplasms.

In light of the evolving experience with oral cavity SCCs after prolonged exposure to PLD, salient features for their occurrence are summarized below. Addressing implications for

patient management and preventive measures beyond raised awareness are the central areas of concern going forward.

Maintenance PLD: A Causative Role?

All 11 recently reported patients (Table 1) share one common feature: treatment with PLD for recurrence of their cancers from 2 years to exceeding 10 years. In terms of cumulative doses of this doxorubicin exposure, the lowest was 720 mg/m² with two exceeding 3,000 mg; the median in the nine patients for whom some estimate could be provided was 2,116 mg. Five of the patients were receiving PLD at the time their SCC or dysplasia was diagnosed, while information is missing in two. Other drug exposures reflect the management of the primary diagnosis, but cyclophosphamide (in two) and platinum (in six), as well as radiation (in one), have been known to be associated with development of secondary malignancies. One of the reports [15] points to the selective accumulation leading to chronic exposure of doxorubicin in the oral mucosa as a causative factor [16].

Genetic Background

Three of the seven patients with gynecologic cancers had BRCA1 mutations, and one had a BRCA2 mutation; as for the four nongynecologic patients, only one had BRCA status reported and it was negative [17]. We have cautioned that because BRCA mutation carriers have better outcomes to platinum [4], as well as to PLD [18], they would be expected to be overrepresented in any reports of patients with long-term follow-up. Nevertheless, it is also likely that any cumulative DNA damage might lead to other forms of repair deficiency adding to the risk of carcinogenesis. As noted by Bonomi et al. [15], familial adenomatous polyposis (FAP) patients have also been linked to secondary malignancies arising in the pancreas and thyroid, but to date not to oral SCCs. As for giant cell tumors of bone [19], no consistent genetic alterations have emerged, although downregulation of the RUNX3 tumor suppressor gene located in 1p36 has been implicated [20].

Immunosuppression and Other Factors

Secondary neoplasms associated with HIV infection were identified early during the AIDS epidemic [21] and again after successful treatment of KS with PLD. The tolerance to this doxorubicin formulation coupled with improvements in survival of HIV patients presumably increased the chance for the development of cancers; in one report, these included principally lymphomas, but also an SCC of the esophagus and one SCC of the tongue [2].

Correspondence: Franco Muggia, M.D., New York University Cancer Institute, 550 First Avenue, New York, New York 10016, USA. e-mail: Franco.Muggia@nyumc.org Received January 12, 2013; accepted for publication January 24, 2013; first published online in *The Oncologist Express* on March 13, 2013. ©AlphaMed Press 1083-7159/2013/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2013-0021>

Table 1. Salient features of individual reported cases of secondary squamous cell carcinoma (SCC)

Reference	Age ^a /sex	First cancer diagnosis and therapies	PLD cumulative mg	SCC site TN stage	Treatment and outcome	Other factors
Cannon et al. [7]	76/F	Tubal: Cis/PLD and IP FUDR; PLD ^b	1,800	Tongue T1N0	S→R, recur, S died, 9 m	None
Cannon et al. [7]	67/F	Ov: CarT; TopoPLD→PLD ^b	2,320	Sublingual dysplasia	S, NED 3 + yr	BRCA1mu
Cannon et al. [7]	52/F	Ov: CarCyT; HIPEC; carPLD→PLD ^b	3,000	Multiple oral T1N0	S→R, local recur, C, S, died, 11 m	BRCA2mu
Cannon et al. [7]	71/F	Ov: CarT→IPcis; carPLD→PLD ^b	2,116	Tongue T1N0	S, NED 2.5 + yr	BRCA1mu
Cannon et al. [7]	54/F	Ov: CarT; IPcisTopo; PLD; Cy+velaparib→bev	1,676	Gingiva T1N0	S: NED 1 + yr	BRCA1mu, Skin SCCs
Ben-David et al. [8]	66/F	Ov: NS: 7 yr on PLD	?	Maxilla	?	None
Ben-David et al. [8]	63/F	KS: NS: 4 yr on PLD	?	Maxilla	?	None
Bonomi et al. [15]	35/M	Desmoid: PLD 40 mg/m ² q4w × 2 yr; [SCC 5y later]	960/m ²	Tongue T1N2b	S→R	FAP/ Gardner's
Bonomi et al. [15]	47/M	Pulmonary KS: PLD 20 mg/m ² 4–8 wk 3 yr [SCC 6 yr later]	>720/m ²	Tongue T3N2b	S→R	HIV, neg HPV
Matsuo et al. [17]	57/F	UPSC: CarT→R; PLD, ^b BrR	3,924	Buccal T4bN0	R→C died 4 m	Brain R
Gu et al. [19]	28/F	Giant cell bone: PLD→denosumab [SCC 3 yr after PLD]	1,260	Tongue T1N0	S: NED status	Smoking, slight

^aAge when diagnosed with SCC.^bOn PLD when SCC or high-grade dysplasia was diagnosed.

Abbreviations: BrR, brain radiotherapy; Cis, cisplatin; FAP, familial adenomatous polyposis; FUDR, floxuridine; HIPEC, heated intraperitoneal chemoperfusion; HIV, human immunodeficiency virus; HPV, human papillomavirus; m, months; KS, Kaposi's sarcoma; NED, no evidence of disease; neg, negative; Ov, ovarian; PLD, pegylated liposomal doxorubicin; SCC, squamous cell carcinoma; Topo, topotecan; UPSC, uterine papillary serous carcinoma; wk, weeks; yr, years.

Two patients (Table 1) had been treated for KS before the diagnosis of oral SCC: one [8] after 4 years on PLD, and the other [15] after 3 years of PLD treatment followed by a 6-year hiatus. In another patient [7], skin damage from ultraviolet light in a very fair individual was associated with the presence of multiple skin SCCs at a time when a gingival SCC was identified.

CONCLUSIONS AND IMPLICATIONS FOR MANAGEMENT

The 11 patients with oral cavity SCCs as secondary neoplasms, described in Table 1, likely represent instances of a pathogenesis that differs from those arising from exposure to smoking or HPV-related oncogenesis. Molecular analyses of these oral cavity tumors are needed to confirm that these SCCs have molecular signatures distinct from those related to smoking or HPV infection. The limited therapeutic experience with these secondary tumors to date does not allow firm conclusions about their management. Documentation of three recurrences, during or shortly after postoperative radiation, raises

the possibility that these secondary tumors may be less sensitive to conventional doses of radiation. On the other hand, surgery achieved excellent control of disease in at least three patients.

Awareness of factors associated with enhanced susceptibility to develop secondary SCCs must begin upon exposure to PLD continuing beyond 1 year. At present, it seems prudent to engage patients in a discussion of risks (of a secondary cancer) versus benefits (of delaying the recurrence of the primary cancer). In addition, oncologists must alert patients after any prolonged PLD exposure to report the presence of any mouth sores, query regarding any oral discomfort, and initiate periodic examinations.

DISCLOSURES

Franco Muggia: Bayer, Eli Lilly, Roche (C/A).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- Hengge UR, Esser S, Rudel HP et al. Long-term chemotherapy of HIV-associated Kaposi's sarcoma with liposomal doxorubicin. *Eur J Cancer* 2001;37:878–883.
- Martín-Carbonero L, Palacios R, Valencia E et al. Long-term prognosis of HIV-infected patients with Kaposi sarcoma treated with pegylated liposomal doxorubicin. *Clin Infect Dis* 2008;47:410–417.
- Andreopoulou E, Gaiotti D, Kim E et al. Pegylated liposomal doxorubicin HCL (PLD; Caelyx/Doxil): Experience with long-term maintenance in responding patients with recurrent epithelial ovarian cancer. *Ann Oncol* 2007;18:716–721.
- Muggia F, Cannon T, Safra T et al. Delayed neoplastic and renal complications in women receiving long-term chemotherapy for recurrent ovarian cancer. *J Natl Cancer Inst* 2011;103:160–161.
- Verschraegen CT, Czok S, Muller CY et al. Phase II study of bevacizumab with liposomal doxorubicin for patients with platinum- and taxane-resistant ovarian cancer. *Ann Oncol* 2012;23:3104–3110.
- Cannon TL, Muggia F, Hirsch EA et al. Multiple cases of squamous cell carcinoma of the tongue and oral cavity in patients treated with long-term pegylated liposomal doxorubicin (PLD) for ovarian cancer. *J Clin Oncol* 2011;15(suppl):5557a
- Cannon TL, Lai DW, Hirsch D et al. Squamous cell carcinoma of the oral cavity in nonsmoking women:

A new and unusual complication of chemotherapy for recurrent ovarian cancer. *The Oncologist* 2012;17:1541–1546.

8. Ben-David Y, Leiser Y, Kacta O et al. Does long-term treatment with Doxil predispose patients to oral cancer? *Int J Clin Oncol* 2012 [Epub ahead of print].

9. Praga C, Bergh J, Bliss J et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: Correlation with doses of epirubicin and cyclophosphamide. *J Clin Oncol* 2005;23:4179–4191.

10. Josting A, Wiedenmann S, Franklin J et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: A report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003;21:3440–3446.

11. Shearer P, Kapoor G, Beckwith JB et al. Secondary acute myelogenous leukemia in patients previously treated for childhood renal tumors: A report from the National Wilms Tumor Study Group. *J Pediatr Hematol Oncol* 2001;23:109–111.

12. Paulussen M, Ahrens S, Lehnert M et al. Second malignancies after ewing tumor treatment in 690 patients from a cooperative German/Austrian/Dutch study. *Ann Oncol* 2001;12:1619–1630.

13. Mays AN, Osherooff N, Xiao Y et al. Evidence for direct involvement of epirubicin in the formation of chromosomal translocations in t(15;17) therapy-related acute promyelocytic leukemia. *Blood* 2010;115:326–330.

14. Mistry AR, Felix CA, Whitmarsh RJ et al. DNA topoisomerase II in therapy-related acute promyelocytic leukemia. *N Engl J Med* 2005;352:1529–1538.

15. Bonomi MR, Misiukiewicz K, Posner M et al. Squamous cell carcinoma of the oral tongue in two patients previously exposed to long-term pegylated liposomal doxorubicin. *The Oncologist* 2012;17:1594–1595.

16. Harrington KJ, Mohammadtaghi S, Uster PS et al. Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeled pegylated liposomes. *Clin Cancer Res* 2001;7:243–254.

17. Matsuo K, Blake EA, Yessaian AA et al. Long-term pegylated liposomal doxorubicin use and oromaxillary squamous cell carcinoma in endometrial cancer. *The Oncologist* 2012;17:1598–1599.

18. Safra T, Borgato L, Nicoletto MO et al. BRCA mutation status as determinant of outcome in women with recurrent epithelial ovarian cancer treated with pegylated liposomal doxorubicin. *Mol Cancer Ther* 2011;10:2000–2007.

19. Gu P, Wu J, Sheu M et al. Aggressive squamous cell carcinoma of the oral tongue in a woman with metastatic giant cell tumor treated with pegylated liposomal doxorubicin. *The Oncologist* 2012;17:1596–1597.

20. Han YX, Liang DY. The role of the tumor suppressor RUNX3 in giant cell tumor of the bone. *Int J Oncol* 2012;40:673–678.

21. Levine AM, Gill PS, Muggia F. Malignancies in the acquired immunodeficiency syndrome. *Curr Probl Cancer* 1987;11:209–255.

EDITOR'S NOTE: This commentary relates to a series of articles and letters published in the December 2012 issue of the journal, which describe the potential role of long-term exposure to pegylated liposomal doxorubicin in the occurrence of squamous cell carcinomas of the oral cavity. We invite you to read the entire series:

Bonomi MR, Misiukiewicz K, Posner M et al. Squamous cell carcinoma of the oral tongue in two patients previously exposed to long-term pegylated liposomal doxorubicin. *The Oncologist* 2012;17:1594–1595.

Cannon TL, Lai DW, Hirsch D et al. Squamous cell carcinoma of the oral cavity in nonsmoking women: A new and unusual complication of chemotherapy for recurrent ovarian cancer? *The Oncologist* 2012;17:1541–1546.

Gu P, Wu J, Sheu M et al. Aggressive squamous cell carcinoma of the oral tongue in a woman with metastatic giant cell tumor treated with pegylated liposomal doxorubicin. *The Oncologist* 2012;17:1596–1597.

Matsuo K, Blake EA, Yessaian AA et al. Long-term pegylated liposomal doxorubicin use and oromaxillary squamous cell carcinoma in endometrial cancer. *The Oncologist* 2012;17:1598–1599.

Also in this series was an article exploring the possible role of PLD in renal thrombotic microangiopathy in ovarian cancer patients:

Kwa M, Baumgartner R, Shavit L et al. Is renal thrombotic angiopathy an emerging problem in the treatment of ovarian cancer recurrences? *The Oncologist* 2012;17:1534–1540.