



Olaratumab administered in two cases of phyllodes tumour of the breast: end of the beginning?

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To cite: Kyriazoglou A, Zagouri F, Dimopoulos MA. Olaratumab administered in two cases of phyllodes tumour of the breast: end of the beginning? *ESMO Open* 2019;4:e000479. doi:10.1136/esmoopen-2018-000479

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Received 4 December 2018

Revised 7 January 2019

Accepted 11 January 2019

ABSTRACT

Phyllodes tumours of the breast are rare mesenchymal tumours with differential malignant potential. Treatment of choice is radical excision with negative margins. Radiation therapy has shown controversial results in small series. Chemotherapy in the adjuvant setting still remains a matter of debate. Doxorubicin-based chemotherapy is recommended for breast sarcomas' first-line treatment. Herein we present two cases of breast phyllodes tumour treated with the recent combination of doxorubicin and olaratumab.

INTRODUCTION

Phyllodes tumours of the breast, previously so-called cystosarcoma phyllodes, are mesenchymal tumours with differential malignant potential.^{1,2} The WHO classification defines them as benign, borderline and malignant tumours.²

Treatment of these tumours is primarily radical surgical resection of the tumour without lymph node dissection. Resection with negative margins (R0) is the mainstay for the surgical management of these tumours. Re-excision of the tumour should be addressed when surgery results to R1 or R2 resection.^{3,4}

Radiation therapy to breast phyllodes tumours has been studied in very few prospective clinical trials.⁵ Several publications in small retrospective series have reported contradictory results. Radiation therapy is applied due to high percentage incidence of recurrences.^{6,7}

Chemotherapy in the adjuvant setting still remains a matter of debate similarly in the soft tissue sarcomas.^{8,9} In the metastatic setting, doxorubicin plus ifosfamide is the most common regimen used.^{10–12} Small series and single cases of metastatic breast phyllodes tumours published report the use of doxorubicin-based systemic chemotherapy.^{13–16} Liposomal doxorubicin in combination with bevacizumab has been reported in one case.¹⁷ In an Indian report, epirubicin with ifosfamide was administered to four patients.¹⁸ Due to the rarity of the disease, there is no

Key questions

What is already known about this subject?

- ▶ Phyllodes tumours of breast are rare mesenchymal tumours with surgical excision being the mainstay of their treatment.
- ▶ There is no consensus on the treatment of metastatic phyllodes tumours due to the rarity of the disease.
- ▶ Systemic chemotherapy with doxorubicin-based regimens is commonly used in the metastatic setting.

What does this study add?

- ▶ This is the first report of two patients with breast phyllodes tumours treated with first-line chemotherapy combination of doxorubicin and olaratumab with poor outcome.
- ▶ The preliminary data presented here suggest the possibility that breast phyllodes tumours might not be highly sensitive to olaratumab.

How might this impact on clinical practice?

- ▶ Prospective studies including histological and molecular characteristics or specific biomarkers in large patient populations might prove to be important predictors of response to olaratumab treatment.

consensus on the systemic treatment of these tumours and patients are treated according to National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) sarcoma guidelines.^{8,9} When disease progression happens, trabectedin and pazopanib are reasonable options.^{19,20}

Olaratumab is an IgG1 monoclonal antibody targeting platelet-derived growth factor receptor alpha (PDGFR α) thus blocking PDGF-AA, PDGF-BB and PDGF-CC binding and receptor activation. Recently, the combination of doxorubicin with olaratumab in metastatic or unresectable doxorubicin-naïve patients with sarcoma studied in a phase Ib-II clinical trial showed an improvement in the median overall survival (OS) of 11.8 months, compared with those patients who received doxorubicin monotherapy.²¹ These results lead to a phase III clinical trial which is highly

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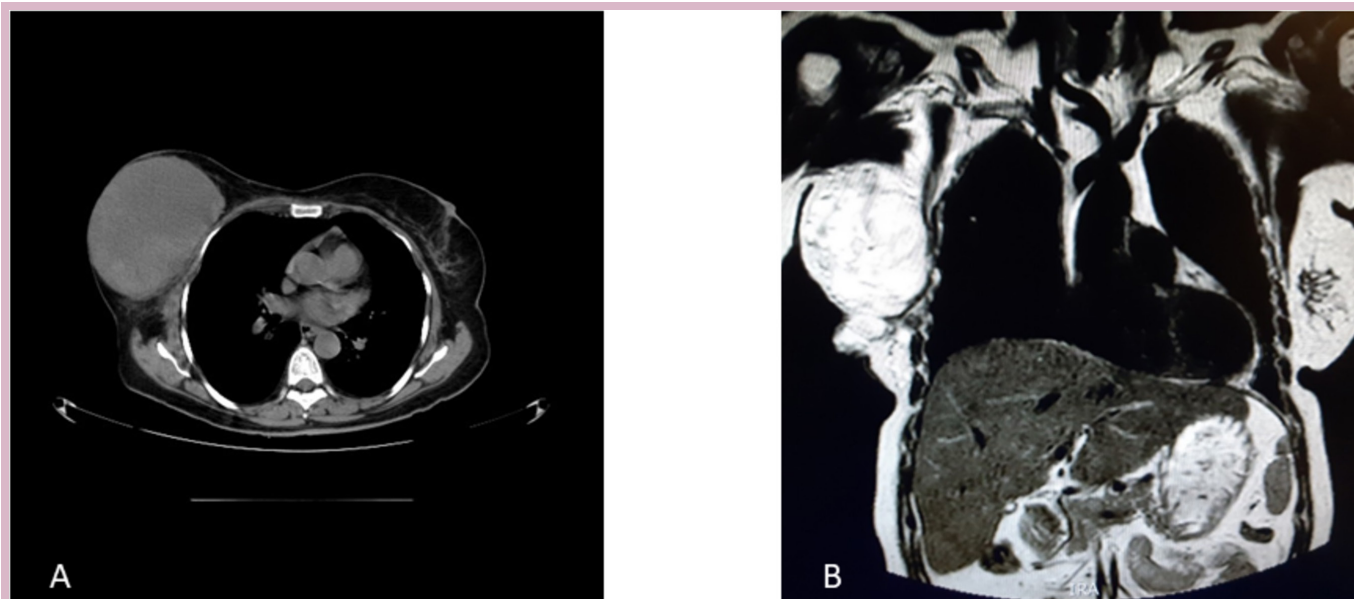


Figure 1 (A) Preoperative chest CT scan revealing a 13×9 cm of the right breast. (B) Postmastectomy chest MRI showing a recurrent tumour mass with satellite lesions connected to the right thoracic wall.

expected to be announced soon. From the 65 patients treated with olaratumab in the aforementioned clinical trial, no patients with breast phyllodes tumour were included.

Herein we present two cases of patients with metastatic breast phyllodes tumour who received first-line chemotherapy with doxorubicin plus olaratumab. Consent was obtained from both patients to report their cases.

PATIENTS AND METHODS

Case 1

In June 2018, a 64-year-old woman presented with a swelling mass on her right breast. Imaging with CT scans of her abdomen and chest described a mass of 13×9 cm in her right breast and nodules of the middle lobe on the right lung with a diameter of 5 mm (figure 1). Tumour biopsy revealed a mesenchymal lesion with morphological characteristics of phyllodes tumour. The patient underwent tumour excision, which favoured the diagnosis of a sarcoma not otherwise specified, originating from a phyllodes tumour. The tumour specimen included sites of necrosis and mitotic index was 25 mitoses/10 high power fields. Immunohistochemistry was positive for Vimentin and CD10 and negative for Desmin, Pck, CK5/6, CD34, Ckit, ER and h-Caldesmin. Due to large extension of the tumour, right mastectomy was performed, which in the pathology report resulted to R1 excision. The patient had an unresectable locally advanced breast sarcoma and subsequently was administered doxorubicin (75 mg/m² day 1) plus olaratumab (15 mg/kg days 1 and 8) and received one cycle, without any toxicities. On day 1 of cycle 2, there was a rapid clinical deterioration, with the presentation of an excessive mass on the right thoracic wall. New imaging confirmed the progression of her

disease with the presence of a 13 cm diameter tumour mass and new satellite lesions especially on the thoracic wall (figure 1). A new lesion on her low lobe of the right lung was also revealed. The patient decided the option of re-excision of the recurrent tumour on a different surgical centre. She deteriorated rapidly and is now offered best supportive care.

Case 2

In November 2017, a 59-year-old woman presented with a growing mass on her right breast. The patient underwent mastectomy with lymphadenectomy. The pathology report revealed phyllodes tumour without metastasis to the excised lymph nodes. Immunohistochemistry was positive for CD34, CD99, CD56, Vimentin, BCL-2 and CD10, while it was negative for EMA, S-100, Desmin, LCA and CD117. The tumour specimen included sites of necrosis and mitotic marker Ki67 was 70%. Due to increased pain in her left thigh, a CT scan was performed showing a pathological fracture caused by a lytic bone lesion (figure 2). Biopsy from the bone revealed a metastatic lesion from a malignant phyllodes tumour and subsequently she received local radiotherapy with a total dose of 30 Gy. Chest CT showed numerous metastatic lesions to both lungs (figure 2). Brain MRI revealed a bone lesion with development of tumour mass on the left parietal bone (figure 2). She received local radiotherapy with a total dose of 30 Gy. The patient was started first-line chemotherapy with doxorubicin (75 mg/m² day 1) and olaratumab (15 mg/kg days 1 and 8), without any toxicities. After three cycles of this combination, restaging with imaging showed progression of her disease with new lung metastases and increase in the size of the already existing and a new lesion on the left gluteal place. The patient

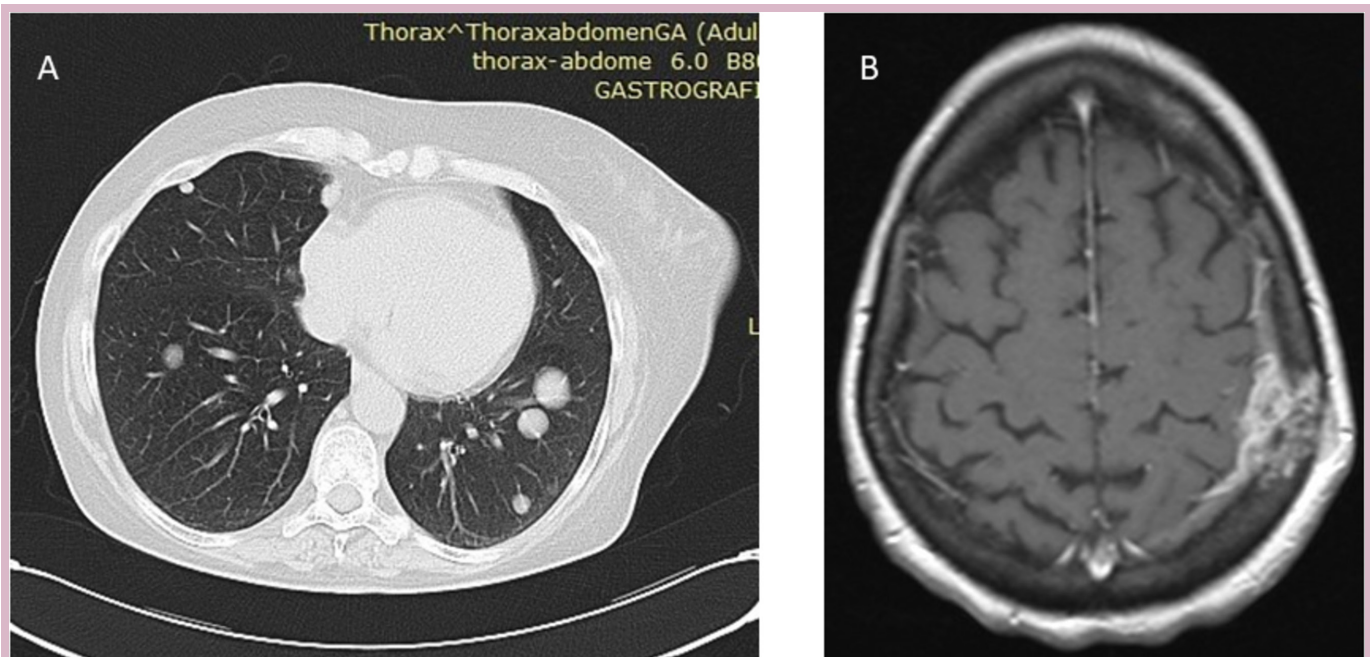


Figure 2 (A) Chest CT scan with multiple metastatic lesions. (B) Brain MRI showing bone lesion with development of tumour mass on the left parietal bone.

was administered trabectedin (1.5 mg/m^2 every 3 weeks). After three cycles of trabectedin new imaging revealed disease progression to both her chest and abdomen with new liver and pancreatic metastases and deterioration of the existing lesions. Third-line chemotherapy with the combination of docetaxel (75 mg/m^2 day 8) and gemcitabine (900 mg/m^2 days 1 and 8) is given with stabilisation of the disease after three cycles.

DISCUSSION

Breast phyllodes tumours are rare mesenchymal malignancies.²² The core element of their treatment is still surgical. Tumour excision with negative margins is the primary goal of the treatment.^{1 3} Adjuvant radiotherapy and chemotherapy are not the standard of care with small retrospective series showing controversial results.^{5 8 9}

Doxorubicin and olaratumab combination has recently been reported showing improvement in the median OS of 11.8 months in patients who received the doublet compared with those patients who received doxorubicin monotherapy.²¹ Recent versions of NCCN and ESMO guidelines included this combination for the first-line treatment of metastatic or unresectable doxorubicin-naïve patients with sarcoma.^{8 9} Interestingly, ESMO guideline members comment on the unknown mechanism of action of olaratumab and the fact that this combination was compared with doxorubicin alone and not with doxorubicin plus ifosfamide, which is the standard of treatment in Europe.⁸ Furthermore, Judson and van der Graaf have raised several questions regarding the discrepancy of the relatively small benefit in progression-free survival (2.6 months) and the great benefit in OS (11.8 months) in this trial.²³ This phase Ib-II clinical

trial studied 65 patients on the arm of the combination of doxorubicin with olaratumab. However, there were not any patients with breast sarcoma included.

We are the first to report the administration of the combination of doxorubicin with olaratumab in two patients with phyllodes tumour of the breast. Both the patients progressed very early during their treatment with doxorubicin and olaratumab. Even though the number of patients treated with this combination is extremely small, it is intriguing to hypothesise that the efficacy of olaratumab to breast phyllodes tumours might be limited. The preliminary data presented here suggest the possibility that breast phyllodes tumours might not be highly sensitive to olaratumab. Especially, the rapid progression of the disease in such a short period from the beginning of olaratumab administration is indicative of a disease with refractorial response to this treatment. The complex and heterogeneous genetic profile of these tumours²⁴ implies the possibility that PDGFR inhibition might not be a principal molecular mechanism for their evolution.^{21 25} Consequently, targeting PDGFR does not seem to add value to their treatment, while ifosfamide, which is the alternative regimen combined with doxorubicin, seems to be more active to these tumours.¹⁶ However, it must be noted that histological and/or molecular characteristics and specific biomarkers tested in large patient populations might prove to be important predictors of response to olaratumab treatment.

The results of the phase III clinical trial of doxorubicin plus olaratumab are highly expected. The administration of this combination in larger amount of patients with subgroup analyses according to several sarcoma histologies is awaited in order to clarify the best responders to

this undoubtedly effective regimen. Hopefully, in this phase III trial, patients with breast sarcoma and more specifically patients with breast phyllodes tumour may be represented adequately, answering the question whether olaratumab should be used in their treatment.

Breast phyllodes tumours are still a neglected sibling of the soft tissue sarcomas. Prospective clinical trials and thorough translational research are unmet needs on the way to a more effective treatment of these aggressive tumours.

Contributors AK was the primary writer of the article and with FZ codirected the study including data analysis and interpretation. MAD contributed to conception and design and was involved in drafting the manuscript and revising it critically for important intellectual content. All authors have read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MAD has received honoraria and advisory board participation from BMS, Celgene, Amgen, Takeda and Janssen. FZ has received honoraria from Roche, Novartis and Lilly.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available upon request.

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REFERENCES

1. Strode M, Khoury T, Mangieri C, *et al.* Update on the diagnosis and management of malignant phyllodes tumors of the breast. *Breast* 2017;33:91–6.
2. Adam M-J, Bendifallah S, Kalhorpour N, *et al.* Time to revise classification of phyllodes tumors of breast? Results of a French multicentric study. *Eur J Surg Oncol* 2018;44:1743–9.
3. Choi N, Kim K, Shin KH, *et al.* Malignant and borderline phyllodes tumors of the breast: a multicenter study of 362 patients (KROG 16-08). *Breast Cancer Res Treat* 2018;171:335–44.
4. Reinfuss M, Mitúš J, Duda K, *et al.* The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. *Cancer* 1996;77:910–6.
5. Barth RJ, Wells WA, Mitchell SE, *et al.* A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. *Ann Surg Oncol* 2009;16:2288–94.
6. Gnerlich JL, Williams RT, Yao K, *et al.* Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer data base, 1998–2009. *Ann Surg Oncol* 2014;21:1222–30.
7. Pandey M, Mathew A, Kattoor J, *et al.* Malignant phyllodes tumor. *Breast J* 2001;7:411–6.
8. Casali PG, Abecassis N, Bauer S, *et al.* Soft tissue and visceral sarcomas: ESMO–EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018;29(Supplement_4):iv51–67.
9. von Mehren M, Randall RL, Benjamin RS, *et al.* Soft tissue sarcoma, version 2.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16:536–63.
10. Narayanakar RP, Gangaiah DM, Althaf S, *et al.* Cystosarcoma phyllodes: pathological enigma: a retrospective review of 162 cases. *Indian J Cancer* 2015;52:365–8.
11. Guillot E, Couturaud B, Reyal F, *et al.* Management of phyllodes breast tumors. *Breast J* 2011;17:129–37.
12. Haberer S, Laé M, Seegers V, *et al.* [Management of malignant phyllodes tumors of the breast: the experience of the Institut Curie]. *Cancer Radiother* 2009;13:305–12.
13. Shan J, Zhang S, Wang Z, *et al.* Breast malignant phyllodes tumor with rare pelvic metastases and long-term overall survival: a case report and literature review. *Medicine* 2016;95:e4942.
14. Ramakant P, Selvamani TMM, Therese MM, *et al.* Metastatic malignant phyllodes tumor of the breast: an aggressive Disease-Analysis of 7 cases. *Indian J Surg Oncol* 2015;6:363–9.
15. Ossa CA, Herazo F, Gil M, *et al.* Phyllodes tumor of the breast: a clinic-pathologic study of 77 cases in a Hispanic cohort. *Colomb Med* 2015;46:104–8.
16. Mitúš JW, Blecharz P, Walasek T, *et al.* Treatment of patients with distant metastases from phyllodes tumor of the breast. *World J Surg* 2016;40:323–8.
17. Su CC, Chen C-J, Kuo S-J. Effect of Lipodox in combination with bevacizumab in a patient with a metastatic malignant phyllodes breast tumor: a case report. *Oncol Lett* 2017;14:6685–9.
18. Mallick S, Joshi NP, Roy S, *et al.* Malignant and borderline phyllodes tumor of Breast treated with a multi-modality approach in a tertiary cancer care centre in North India. *South Asian J Cancer* 2016;5:1–3.
19. van der Graaf WTA, Blay J-Y, Chawla SP, *et al.* Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879–86.
20. Gordon EM, Sankhala KK, Chawla N, *et al.* Trabectedin for soft tissue sarcoma: current status and future perspectives. *Adv Ther* 2016;33:1055–71.
21. Wagner AJ, Kindler H, Gelderblom H, *et al.* A phase II study of a human anti-PDGFR α monoclonal antibody (olaratumab, IMC-3G3) in previously treated patients with metastatic gastrointestinal stromal tumors. *Ann Oncol* 2017;28:541–6.
22. Lim SZ, Ong KW, Tan BKT, *et al.* Sarcoma of the breast: an update on a rare entity. *J Clin Pathol* 2016;69:373–81.
23. Judson I, van der Graaf WT. Sarcoma: Olaratumab - really a breakthrough for soft-tissue sarcomas? *Nat Rev Clin Oncol* 2016;13:534–6.
24. Kim J-Y, Yu JH, Nam SJ, *et al.* Genetic and clinical characteristics of phyllodes tumors of the breast. *Transl Oncol* 2018;11:18–23.
25. Vincenzi B, Badalamenti G, Napolitano A, *et al.* Olaratumab: PDGFR- α inhibition as a novel tool in the treatment of advanced soft tissue sarcomas. *Crit Rev Oncol Hematol* 2017;118:1–6.