Medical Oncology (2019) 36:4
https://doi.org/10.1007/s12032-018-1228-y

SHORT COMMUNICATION

Radiotherapy with the anti-programmed cell death ligand-1 immune checkpoint blocker avelumab: acute toxicities in triple-negative breast cancer

Eliana La Rocca[1,2] · Michela Dispinzieri[1,2] · Laura Lozza[1] · Gabriella Mariani[3] · Serena Di Cosimo[4] · Massimiliano Gennaro[5] · Riccardo Valdagni[6] · Maria Carmen De Santis[1]

Received: 9 October 2018 / Accepted: 13 November 2018 / Published online: 15 November 2018

Abstract

Triple-negative breast cancer (TNBC) is clinically the most aggressive breast cancer (BC) subtype. There is an urgent need for effective therapies for patients with TNBC. Recent findings confirm the important role of factors related to the immune system in the clinical outcome and response to treatment of TNBC patients. Avelumab selectively binds to PDL1, and competitively blocks its interaction with anti-programmed death 1 (anti-PD-1) antibodies. Unlike anti-PD-1 antibodies, which target T-cells, avelumab targets tumor cells, and is therefore expected to have fewer side effects, including a lower risk of Immune-Related Adverse Events (irAEs). Uncertainties remain regarding a potential synergy resulting in increased toxicities by combining radiotherapy and immune-checkpoint inhibitors (ICIs). Effects of concomitant ICIs with thoracic radiotherapy on pulmonary toxicities is not currently known. There are no published data available on the effects of combining anti-PD-L1 with adjuvant radiotherapy (RT) for BC in a clinical setting. We reported a preliminary experience on the first patient treated at the National Cancer Institute of Milan with the association of avelumab and concomitantly RT for TNBC.

Keywords Breast cancer · Concomitant radiotherapy · Immunotherapy · Safety · Pulmonary toxicity

Viewpoints and debates

Triple-negative breast cancer (TNBC) accounts for 10–20% of all cases of breast cancer (BC), and it is clinically the most aggressive BC subtype. It is associated with such unfavorable clinicopathological features as a high tumor grade, basal cytokeratins 5/6, p53 overexpression, BRCA1 mutations, younger age at onset, cell necrosis, large tumor size, and high mitotic indices. Compared with other molecular subtypes, TNBC carries the worst locoregional recurrence rates (LRR) in the first three years after treatment. It is often associated with distant metastasis and the associated 5-year mortality rate is high [1]. The risks of recurrence and mortality are significantly lower in TNBC patients who achieve a complete pathological response (pCR) [2]. Several authors recently sought to identify prognostic gene expression profiles in TNBC, finding a better prognosis in patients with a high expression of genes related to the immune system [3]. Immune genes were also reportedly associated with sensitivity to chemotherapy [4]. Taken together, these findings confirm the important role of factors related to the immune system in the clinical outcome and response to treatment

✉ Maria Carmen De Santis
mariacarmen.desantis@istitutotumori.mi.it

1 Radiotherapy Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

2 Department of Oncology and Hemato-oncology, Università degli Studi di Milano, Milan, Italy

3 Department of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

4 Department of Applied Research and Technological Development (DRAST), Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

5 Breast Surgery Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

6 Department of Oncology and Hemato-oncology, Radiation Oncology 1 and Prostate Cancer Program, Università degli Studi di Milano, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

of TNBC patients. It is common knowledge that TNBC is highly immunogenic, largely because of its genetic instability. As a consequence, high mutational load mutated proteins are more readily recognized by the immune system than non-mutated ones, and may increase the pool of tumor-associated neo-antigens. By comparison with other BC subtypes, TNBC is therefore more likely to be infiltrated by immune cells, and especially tumor-infiltrating lymphocytes (TILs).

TILs are of prognostic significance in patients with TNBC [5]. On these premises, immunotherapies seem very promising for this subset of high-risk patients for whom chemotherapy is the only possible systemic treatment in current clinical practice.

Avelumab is an anti-programmed cell death ligand-1 (PD-L1) immune-checkpoint blocker that can lead to anti-tumor immune response being restored by enhancing tumor infiltration and the production of cytotoxic molecules (IL2 and IFN γ) by T lymphocytes. Avelumab selectively binds to PD-L1, and competitively blocks its interaction with anti-programmed death 1 (anti-PD-1) antibodies. Unlike anti-PD-1 antibodies, which target T-cells, avelumab targets tumor cells, and is therefore expected to have fewer side effects, including a lower risk of Immune-Related Adverse Events (irAEs). As PD-L1 blockade leaves the PD-L2 to PD-1 pathway intact, it promotes peripheral self-tolerance. Multiple organ systems can be affected by irAEs, including the skin, gastrointestinal tract, liver, kidney, endocrine glands, nervous system, musculo-articular system, eyes, heart, lung and blood cells. Little is known about the incidence of hematological toxicities across published trials. The overall incidence of anemia during PDL1 inhibition was 9.8% for all grades, and 5% for G3–G5 anemia. The incidence of leukopenia, all grades and G3–G5, and of thrombocytopenia were 0.94%, 1.07%, 2.8%, and 1.8%, respectively [6]. The term "pneumonitis", generally used for immune-related adverse events in the lung, covers a wide and overlapping spectrum of pulmonary manifestations and occurs in about 3–5% of patients receiving ICIs. For the time being, few data are available regarding the emerging field of adverse events due to the use of immune-checkpoint inhibitors (ICIs). Uncertainties remain regarding a potential synergy resulting in increased toxicities by combining radiotherapy and ICIs. Effects of concomitant ICIs with thoracic radiotherapy on pulmonary toxicities is not currently known and based on studies conducted in the setting of lung or metastatic cancer [7–9]. A secondary analysis of the KEYNOTE-001 trial [10] compared the pulmonary toxicity according to whether the patient had received any prior radiotherapy. Pulmonary toxicities of any grade were observed more frequently in the patients who had received previous thoracic radiotherapy (63%) versus those did not receive (40%). No differences in grade 3 pulmonary toxicity were noted. Delaunay et al. [11] presented the results of a retrospective study of 1826 cancer patients treated with ICIs. 3.5% of the patients developed interstitial lung diseases (ILDs). ICI-related ILDs are also characterized by a very wide range of clinical and radiological presentations. The most common pattern is organizing pneumonia but this accounts for only one in four cases, followed by hypersensitivity pneumonitis, non-specific interstitial pneumonia, and bronchiolitis. It is essential to identify risk factors for ICI-related ILDs in order to screen patients at higher risk and increase awareness of this potentially life-threatening complication. The mechanisms of this toxicity remain largely unknown [12]. The cohort was mainly composed of lung cancer patients (75%). Most of anticancer treatments currently used in the management of BC may induce some degree of pneumonitis that is estimated to have an incidence of 1–3% [13]. There are no published data available on the effects of combining anti-PD-L1 with adjuvant radiotherapy (RT) for BC in a clinical setting. We reported a preliminary experience on the first patient treated at the National Cancer Institute of Milan with the association of avelumab and concomitantly RT for TNBC.

Clinical case presentation

This clinical report concerns a 48-year-old woman treated at the Italian National Cancer Institute in Milan. The patient has a positive family history of BC, with a diagnosis of TNBC in a 55-year-old cousin. She had one full-term pregnancy and had breastfed her baby. In April 2017, she found two suspect left axillary lymph nodes on self-examination, and in May 2017 she underwent mammography, bilateral mammary ultrasound and magnetic resonance imaging, which revealed a 2 cm suspect nodule in the supero-external quadrant at prepectoral level. Figure 1 shows opacity in the left external prepectoral plane that was visible on the mammogram, and the tumor was clearly visible on contrast-enhanced T1-weighted sequences (Fig. 2). In June 2017, the patient underwent nodule and lymph node core biopsy, and she was diagnosed with TNBC, with a mitotic proliferation of 80%. In July 2017, she underwent quadrantectomy and axillary dissection. Histology confirmed ductal grade 3 carcinoma, TNM stage pT1b (1 cm) N2a (4/20). ER and PgR were negative, HER2 was not overexpressed, and Ki-67 was 80%. Before starting chemotherapy, the patient had a CT scan and a bone scan, which were negative for metastases. She also underwent cardiovascular assessment, with a cardiological examination and echocardiography. The FEVS was 74%, and modest hypertension came to light, which has been treated with 5 mg of ACE inhibitors. In November 2017, the patient started chemotherapy with 4 cycles of doxorubicin and cyclophosphamide, followed by 10 cycles of paclitaxel. The last two cycles of paclitaxel were not administered due to a periungual infection. After

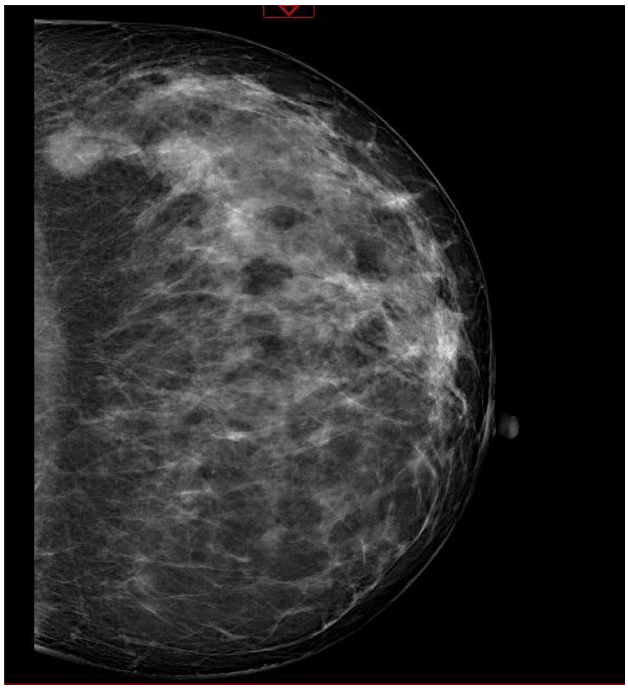

Fig. 1 Mammography

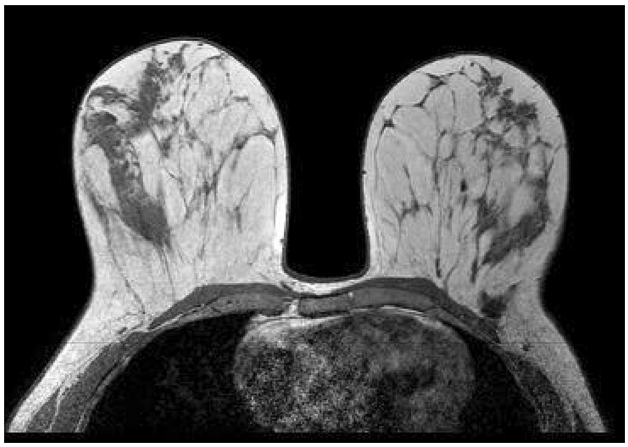

Fig. 2 MRI

the chemotherapy, a repeat CT scan showed centrilobular micronodules with bronchiectasis mainly involving the lung bases, driven by bronchiolitis. Lung function tests revealed a chronic obstructive pulmonary disease with a normal DCLO. A pulmonary consultation did not contraindicate RT or immunotherapy. In April 2018, the patient was randomized to join the experimental arm of a protocol with avelumab 10 mg/kg iv. q2w for 1 year (52 weeks). From April 4th to June 15th she was administered adjuvant RT concomitantly to avelumab (permitted by the protocol), with 50 Gy to the left breast and supra- and infraclavicular lymph nodes, and a boost to the tumor bed, for a total dose of 10 Gy. The RT was administered in daily fractions of 2 Gy. The left breast was treated with two tangential fields, the supra- and infra-clavicular lymph nodes with two opposing fields. The patient reported a grade 3 cutaneous toxicity at the end of the treatment involving an area of moist desquamation in the inframammary fold that resolved in 2 weeks and a grade 1 dysphagia that resolved at the end of RT. Despite the higher risk due to her tobacco exposure and her chronic respiratory disease revealed by lung function tests at the end of chemotherapy, the patient did not develop any acute pneumonitis. A CT scan performed 12 weeks after the end of RT did not reveal any subacute pulmonary toxicity. The follow-up is too short for now, and the patient still risks developing pulmonary fibrosis. During the follow-up, she will continue to undergo clinical and instrumental assessments with lung function tests and CT scans, blood sampling and echocardiography to detect any late irAEs. Figure 3 shows the cosmetic result and the appearance of the breast 3 months later. In particular, the inframammary fold reveals some small areas of telangiectasia with depigmentation. At the time of writing, the patient is alive and disease-free. Although further larger-scale investigations are needed on the toxicity profile of concomitant anti-PDL1 treatment and RT, our very preliminary results are encouraging.

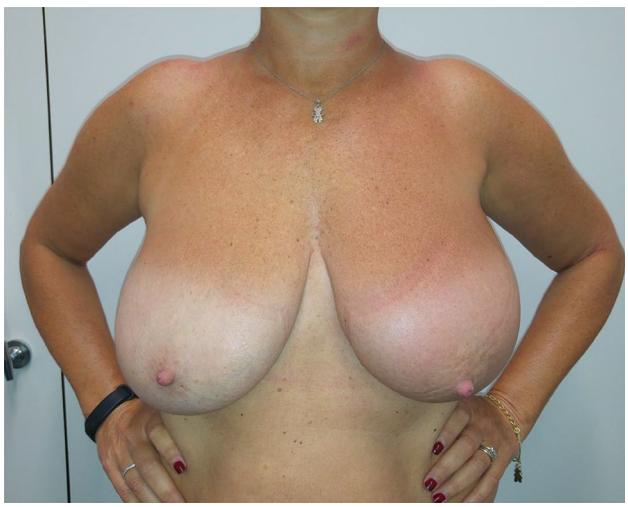

Fig. 3 Aspect of the breast 3 months later

Acknowledgements The Authors would like to thank Prof. P. Conte and Prof. V. Guarneri, the PI and co-PI behind this study.

Compliance with ethical standards

Conflict of interest we have no conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present study has been reviewed and approved by the Ethical Review Board of the National Cancer Institute, Italy.

Informed consent Informed consent for publication of this case study was obtained from the patient concerned.

References

1. Bernier J, Poortmaans PM. Surgery and radiation therapy of triple negative breast cancers: From biology to clinics. Breast. 2016;28:148–55. https://doi.org/10.1016/j.breast.2016.05.014.
2. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–72. https://doi.org/10.1016/S0140-6736(13)62422-8.
3. Jézéquel P, Loussouarn D, Guérin-Charbonnel C, Campion L, Vanier A, Gouraud W, et al. Gene-expression molecular subtyping of triplenegative breast cancer tumours: importance of immune response. Breast Cancer Res. 2015;17:43. https://doi.org/10.1186/s13058-015-0550-y.
4. Desmedt C, Di Leo A, de Azambuja E, Larsimont D, Haibe-Kains B, Selleslags J, et al. Multifactorial approach to predicting resistance to anthracyclines. J Clin Oncol. 2011;29(12):1578–86. https://doi.org/10.1200/JCO.2010.31.2231.
5. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol. 2011;29(12):1578–86. https://doi.org/10.1200/JCO.2010.31.2231.
6. Fausto Petrelli R, Ardito K, Borgonovo, et al. Haematological toxicities with immunotherapy in patients with cancer; a systematic review and metanalysis. Eur J Cancer 2018 103:7–16. https://doi.org/10.1016/j.ejca.2018.07.129.
7. Louvel G, Bahleda R, Ammari S, et al. Immunotherapy and pulmonary toxicities: can concomitant immune-checkpoint inhibitors with radiotherapy increase the risk of radiation pneumonitis? Eur Respir J. 2018;51:1701737. https://doi.org/10.1183/13993003.01737-2017.
8. Kroeze SGC, Fritz C, Hoyer M, Lo SS, Ricardi U, Sahgal A, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. Cancer Treat Rev. 2017;53:25–37. https://doi.org/10.1016/j.ctrv.2016.11.013.
9. Luke JJ, Lemons JM, Karrison TG, Pitroda SP, Melotek JM, Zha Y, et al. Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors. J Clin Oncol. 2018. https://doi.org/10.1200/JCO.2017.76.2229.
10. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol. 2017;18:895–903.
11. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J. 2017;50:1700050.
12. Montani D, Seferian A, Parent F, et al. Immune checkpoint inhibitor-associated interstitial lung diseases: some progress but still many issues. Eur Respir J. 2017;50:1701319.
13. Omarini C, Thanopoulou E, Johnston SR. Pneumonitis and pulmonary fibrosis associated with breast cancer treatments. Breast Cancer Res Treat. 2014;146(2):245–58. https://doi.org/10.1007/s10549-014-3016-5.