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Immunotherapy in Endocrine Responsive Metastatic Breast Cancer

Case Report

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Abstract

Immunotherapy has shown great benefit in multiple tumour types like melanoma and lung cancer. Although breast cancer was previously not considered an immunogenic disease, immunotherapy has recently demonstrated a survival benefit, combined with chemotherapy in metastatic triple negative breast cancer, as well as higher complete pathological response rates when added to chemotherapy in the neoadjuvant setting. There is currently no approval for the use of immunotherapy in endocrine responsive metastatic breast cancer. We present a case of a 34-year-old woman with stage IV endocrine responsive, Her 2 negative breast cancer, who responded to Pembrolizumab, following failure of multiple lines of hormonal blockade and chemotherapy.

Keywords

Tumour infiltrating lymphocytes (TIL); checkpoint inhibitors; microsatellite instability (MSI) breast cancer; PDL 1 expression.

Introduction

Immunotherapy has made great strides in the treatment of cancer, especially in the field of melanoma and lung cancer. Patients with non-small cell lung cancer whose tumours have a>50% PDL 1 expression have superior progression free survival compared to chemotherapy [1]. The combination of chemotherapy and immunotherapy has also shown a progression free and overall survival benefit over chemotherapy alone in first line non-small cell lung cancer regardless of PDL status [2]. In metastatic melanoma the combination of CTLA4 antibodies and check point inhibitors has seen the 5-year survival increase from 10% in the pre-immunotherapy era to in excess of 40% with immunotherapy [3].

Although the presence of tumour-infiltrating lymphocytes (TILs) has been found to be a predictor of response and disease free survival in Her 2 positive and triple negative breast cancer [4] there remains a paucity of data for the use of immunotherapy in endocrine responsive, Her 2 negative breast cancer. TILs are lymphocytes that have migrated from the bloodstream to the tumour,and can be found in the tumour itself and/or in the stroma. They play a role in killing of cancer cells and can be manipulated to augment an anti-tumour response.

Breast cancer has been generally regarded as a non-immunogenic cancer.The responses to immunotherapy have been modest. In March 2019 the first immunotherapy

drug approved by the FDA in breast cancer was Atezolizumab, a PDL 1 inhibitor given in combination with Nab-Paclitaxel in first line metastatic, PDL 1 positive triple negative breast cancer patients on the basis of the IMpassion130 study [5].

Furthermore, in the neoadjuvant setting the combination of a PD1 inhibitor, Pembrolizumab with chemotherapy (KEYNOTE 522 study), showed a higher proportion of complete pathological response, 64.8 % in the Pembrolizumab and chemotherapy combination arm compared to 51.2% in the chemotherapy alone arm [6].

Case report

We report on a female patient diagnosed in 2012, at age 26, with a stage IIB (T2,N1,M0), grade II, invasive ductal cancer of the right breast. She underwent a right sided mastectomy and an axillary node dissection for a 25x30x30mm tumour, 1/9 lymph nodes positive, with extranodal extension. The cancer was ER/PR positive and Her 2 negative. No Ki 67 was available.

The patient underwent adjuvant therapy with 4 cycles of AC(Adriamycin, Cyclophosphamide) followed by 3-weekly Docetaxel, administered at another facility. This treatment was abandoned owing to patient's poor tolerability. She did not undergo radiation treatment.

The patient was then placed on adjuvant hormonal blockade with Tamoxifen, which was stopped at 6 months as a result of a deep vein thrombosis. She was switched to Letrozole and 3-monthly SC Leuprorelin acetate.

She was referred to our Oncology Centre in 2014, whilst on Letrozole and a gonadotropin-releasing hormone agonist, requesting a second opinion and continuation of care. She had no comorbidities.

In February 2016, the patient presented with a localised right axillary mass. A core biopsy was carried out, and the patient was diagnosed with recurrent high grade, poorly differentiated invasive ductal cancer of the breast. Histology showed an ER strongly positive (>66%), PR negative and Her 2 negative cancer. The Ki 67 was 40%, and a prominent TIL population was identified.

A PET-CT scan confirmed the presence of only 2 localized axillary tail masses, measuring 27x20mm and 28x15mm, without evidence of systemic disease.

The patient was discussed at our weekly multidisciplinary breast tumour board meeting,and the decision was made to treat her initially with chemotherapy, followed by surgical excision and adjuvant radio therapy. The patient was treated with weekly Paclitaxel 80/m2. She received 9 out of 12 weekly treatments. Treatment was stopped due to the development of grade 3 sensory peripheral neuropathy.

Following the chemotherapy treatment, the masses were excised with clear margins. Histological examination revealed a 16mm residual invasive ductal cancer,and a second lesion with evidence of only fibrous tissue.3 benign nodes were excised from the right axilla.

The patient underwent radiotherapy to the chest wall and supraclavicular nodes with 50Gy in 25 fractions, followed by a boost of 12Gy in 6 fractions to the tumour bed.

She was then placed on Exemestane and Leuprorelin acetate which she continued for 21 months. At that time, on a routine visit, the patient was found to have an irregular thickening on the right chest wall. A biopsy showed a grade III invasive ductal cancer of a similar immunohisto chemical pattern as the local recurrence diagnosed 2 years prior. Further biomarker testing did not demonstrate micro satellite instability (MSI) but the PDL1 Tumour Proportion Score was high at 95%.

A PET-CT scan showed metastatic bilateral cervical, mediastinal, para-aortic and left external iliac lymphadenopathy, without evidence of visceral disease.

The patient was treated with systemic chemotherapy with a combination of Vinorelbine and Capecitabine. Following 3 cycles of treatment she had achieved a partial response (PR) with a 48% reduction of the lymphadenopathy (shortest diameter asper RECIST 1.1). The patient went on to receive a further 4 cycles, but follow-up CT scans performed showed disease progression,with an increase in size of the mediastinal lymph nodes, and the development of new submandibular nodes.

Due to the previously demonstrated high PDL1 score and after obtaining the patient's consent it was decided to initiate her on single agent Pembrolizumab. After 3 cycles of treatment the patient obtained a PRwith a 42% reduction from baseline(pre-Pembrolizumab). (Figure 1; Figure 2*)* Treatment was continued.

After 10 cycles of Pembrolizumab the patient complained of flu-like symptoms, weight loss of 4kg, an fatigue. Blood tests performed showed a high glucose

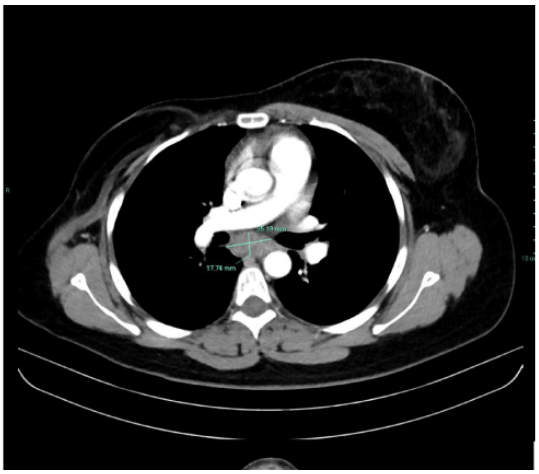

Figure 1

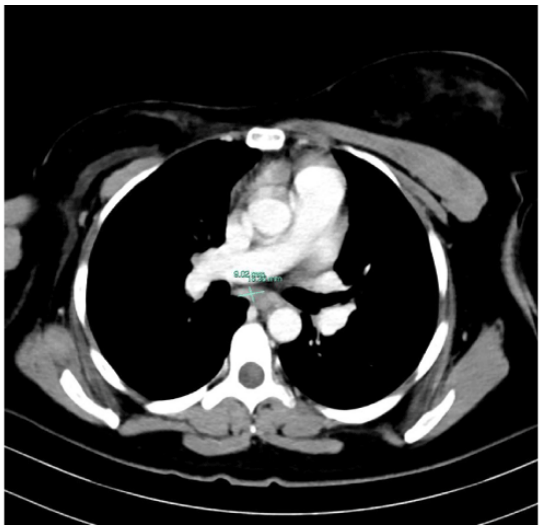

Figure 2

of 20 mmol/L (ref range: 2.2-7.8mmol).The patient was diagnosed with Diabetes Mellitus and referred to an endocrinologist. C-peptide was 442pmol/L(260-1728 pmol/L), Anti GAD antibodies, <5IU/mL(ref <10.0 IU/mL) and Anti IA2 antibodies, <10.0 IU/mL (ref <10.0), allwithin ormallimits. She was initiated on Insulin, with a rapid and good glycemic control.

The Pembrolizumab treatment was resumed once glycemic control was achieved at the then standard dose of 200mg 3 weekly.

During the administration of her 15th cycle the patient complained of a swollen,painful right knee.Clinically, the knee was visibly swollen, hot to the touch, and erythematous.The patient was started on Prednisone and Celecoxib and was referred to a rheumatologist for further treatment of an inflammatory arthritis.

The Pembrolizumab was interrupted until resolution of the arthritis.

At the last visit the patient had no new complaints but follow up CT scans have shown a left adnexal mass suspicious for a Krukenberg tumour.This is currently under investigation.

The patient attained a partial response (PR) with disease control for 18 months, following failure of multiple lines of treatment in the metastatic setting.

Discussion

Immunotherapy represents a major breakthrough in cancer treatment. It has improved outcomes significantly, bringing us closer to a “cure”, like in malignant melanoma. The side effects of this treatment are well known and are mostly as a result of immune hyperactivation. The majority of the side effects are manageable and different from those associated with chemotherapy.

As with many other treatments, patient selection is key to obtain maximal benefit. Subtypes of patients more likely to benefit from these novel agents are yet to be fully defined.

The biomarkers for patient selection for immuno therapy are still under investigation. The IMpassion 130 trial showed an overall survival (OS) benefit of 25 months vs 15.5 months in the PDL 1 positive population. This trial used the Ventana(SP 142) assay as the companion diagnostic for PDL testing [5].

Among the challenges of using PDL1 as a biomarker are tumour heterogeneity, discordance between the PDL1 expression of the primary cancer and the metastases, the cut-off for PDL1 positivity, the different assays available, and differences in PDL1 expression reporting, e.g. reporting PDL1 positivity on membranous staining on tumour cells only, the Tumour Proportion Score(TPS),or reporting PDL 1 positivity on both tumour plus inflammatory cells in the tumour microenvironment, the latter being the Combined Positive Score (CPS).

As an example,the PDL1 CPS score was used in the Keynote 119 study, a phase III randomized trial comparing Pembrolizumab and physician’s choice of chemotherapy, in patients with previously treated in patients with previously

treated metastatic triple negative breast cancer. Although this was overall a negative study, patients with a CPS score of >20 derived an overall survival benefit, with a hazard ratio for OS of 0.58 at 12 months, 95% confidence interval of 0.38-0.88 [7].

The presence of TIL has been shown to correlate with a higher complete pathological response and longer disease-free survival in Her 2 positive and triple negative breast cancers, but also correlates with a detrimental effect on endocrine responsive cancers, suggesting the possibility of a different immune cell phenotype for ER positive breast cancer.

Higher TILs are associated with an overall survival benefit in TNBC but not with Her 2 positive cancers. This data demonstrated that breast cancer is immunogenic, and highlighted the need to explore immune modulating therapies for breast cancer treatment. Furthermore, in the IMPassion130 trial, the majority of tumours that were PDL1 positive were also TIL positive, showing some correlation between PDL 1 positivity and high TIL expression [8].

Mismatch repair (MMR) system is important for genomic stability and cancers that are deficient in MMR proteins have a higher mutation load and a higher likelihood of response to checkpoint inhibitors [9]. In 2019,the FDA approved Pembrolizumab as an agnostic drug for any metastatic cancer that was MSI-H or MMR-deficient on the basis of the KEYNOTE 158 trial [10]. It is known that 15% of colon cancers [11] and 20-30% of endometrial cancers[12] are MMR deficient,but only 2% of breast cancers were in the aforementioned trial, limiting applicability of these results to patients with metastatic breast cancer.

Other biomarkers of interest are immune gene signatures, CD 8 expression and tumour mutation burden, and more data is needed to inform how these may be incorporated in practice to assist future patient selection.

Conclusion

We describe a young patient with metastatic breast cancer, luminal B-like subtype, with a high TIL infiltrate and a PDL1 expression of 95%, who failed endocrine therapy and multiple lines of systemic chemotherapy and responded to subsequent treatment with single agent Pembrolizumab.

However, Pembrolizumab is currently not approved for the treatment of advanced endocrine responsive, Her 2 negative breast cancer. This Case Report shows that there may be other sub groups of patients with metastatic breast cancer who could benefit from immunotherapy. Clinical trials are required to further clarify biomarkers to identify these patients, beyond clinical-pathological classifications.

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