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Revolutions in cancer treatment:
how can they be integrated?

Triple-negative breast cancers

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Abstract

Triple-negative breast cancer (TNBC) is composed of cells that have no oestrogen or progesterone receptors and do not over-express human epidermal growth factor receptor 2 (HER2). Due to the lack of specific targets, chemotherapy is still the main treatment modality for TNBC, but the results are mediocre in comparison with those for other subtypes of breast cancer. A huge amount of clinical research is taking place in the area of TNBC and this article presents the latest clinical trials, particularly those using combined approaches involving chemotherapy and immunotherapy. The results that have been achieved are encouraging for treatment of early stages of the disease, in neoadjuvant treatment and possibly in first-line treatment of metastatic disease. Many different combinations of immunotherapies and targeted therapies are now being evaluated to try to improve the efficacy of treatment; the results should make it possible to develop a treatment strategy that is optimised for patients with TNBC.

Triple-negative breast cancer (TNBC) consists of cells that have no receptors for oestrogen or progesterone or do not overexpress HER2 (human epidermal growth factor receptor 2). It is a distinct type of breast cancer with its own treatment options. The Epidemiological Strategy and Medical Economics (ESME) cohort study, initiated by Unicancer in France, and covering the period from 2012 to 2014, showed that overall survival of patients with metastatic TNBC was 15.7 months.[1] The median overall survival was 13 months for patients who had a recurrence after adjuvant treatment and 21 months for patients with de novo metastatic disease. TNBCs are particularly chemosensitive, but there is a high risk of recurrence. The aim in neoadjuvant setting is to obtain a pathological complete response (pCR), i.e. the absence of invasive cancer cells, after neoadjuvant treatment, because patients with a pCR have a lower risk of recurrence, while the prognosis is poor for patients not showing a pCR.[2]

Immunotherapy is predicated on the theory that neoantigens synthesised by cancer cells induce an immune reaction against the tumour; TNBC is the most immunogenic type of breast cancer. In addition, mutational load may influence this reaction, and breast cancers overall are in the middle of the ranking of cancer types by mutational load[3] with marked differences between luminal A and TNBC. The presence of tumour-infiltrating lymphocytes (TILs) in the breast, either within the tumour or in the stroma, is a good prognostic factor.[4, 5]Amongst the different subtypes of breast cancer, the basal type is most common type of TNBC, and has the most TILs. The presence of TILs also predicts a better response to chemotherapy.[6-9] The use of immunotherapy for treatment of TNBC is therefore justified (**Table 1**).

Table 1. Rationale for the use of immunotherapy for treatment of TNBC

▪ Presence of a lymphocytic infiltrate
▪ Prognostic impact of the lymphocytic infiltrate
▪ Predictive impact of the lymphocytic infiltrate (pathological complete response)
▪ Strong expression of PD-L1: immune cells > tumour cells
▪ High mutation rate
▪ High therapeutic need: absence of targeted therapy in both localised and advanced disease

ANTI-PD-1/PD-L1 MONOTHERAPY

First-line treatment of patients with metastatic TNBC with the anti-programmed death-ligand-1 (PD-L1) agent atezolimumab or the anti-programmed death receptor-1 (PD-1) agent pembrolizumab can achieve response rates of 26% and 23%, respectively,[10, 11] while the response rates fall to 6.5% and 4.7%, respectively, if these are given as second-line treatment. Once patients respond to treatment with immunotherapy, their objective response rate increases and overall survival is longer,[10] which is not usually the case with TNBCs. After the first line of treatment, however, pembrolizumab as monotherapy is no more effective than chemotherapy,[12] except for a small subset of patients whose Combined Positive Score is high (≥20). This score is obtained by dividing the number of PD-L1 positive immune cells (T and B lymphocytes and macrophages) associated with the tumour, by the total number of viable tumour cells in the sample, and multiplying the result by 100. To deal with the poor efficacy of anti-PD-1 monotherapy beyond the first line of treatment, treatment combinations have been developed.

TREATMENT COMBINATIONS

A phase multinational III study, IMpassion 130, has shown that in comparison with nab-paclitaxel monotherapy, mainly used in the USA, the combination of atezolizumab/nab-paclitaxel as first-line treatment in metastatic disease improves progression-free survival for patients with metastatic or inoperable TNBC (7.2 versus 5.5 months with nab-paclitaxel monotherapy).[13] Overall survival in the intention-to-treat patient population was not significantly

different between the two groups (21 months with the combination versus 18.7 months with monotherapy). On the other hand, overall survival seemed to be better in the subpopulation of patients who were PD-L1 positive (25 months with the combination versus 18 months with monotherapy).[14] These results need to be confirmed when the final analysis is carried out, but this combination has been approved in the USA by the Food and Drug Administration (FDA).

The immunogenicity of tumours and of chemotherapies can be classified, and their various clinical actions can be categorised (e.g., induction or first-line or adjuvant).[15, 16] What is the best induction treatment combined with immunotherapy? The TONIC phase II study compared different treatment approaches against placebo: irradiation, cyclophosphamide, cisplatin and doxorubicin. The results of this study have shown that anthracyclines were among the most immunogenic, so the combination of these agents with an anti-PD-1/PD-L1 agent should be really tested over other combinations.[17] A phase III study that is currently in progress (Keynote 355, NCT02819518) is comparing the efficacy of three chemotherapy approaches (nab-paclitaxel, paclitaxel and gemcitabine/carboplatin) in combination with pembrolizumab. The results, which are expected in 2020, should make it possible to determine the best combination for first-line treatment of patients with metastatic TNBC.

Which treatment should be given first when combining immunotherapy and chemotherapy? The results of the GeparNUEVO study have shown that there is little therapeutic benefit when chemotherapy precedes immunotherapy. On the other hand, immunotherapy significantly potentiated the effects of chemotherapy in this study: patients' response rates rose from 41.4% to 61.0%.[18] A trial is being conducted to try and reproduce these results.

In the Keynote 522 phase III trial, patients were given traditional chemotherapy as a sequence of 22 weeks' treatment with a combination of paclitaxel, an anthracycline and carboplatin, together with either pembrolizumab or placebo. These patients then underwent surgery, and subsequently received further treatment with either pembrolizumab or placebo for a total treatment duration of 1 year of immunotherapy. The results showed that the number of patients showing a pCR shifted from 50% to 65% when using a combination of chemotherapy + pembrolizumab as neoadjuvant treatment.[19] The proportion of PD-L1 positive patients showing a pCR was 68.9% (versus 54.9% in the placebo group); fewer PD-L1 negative patients had a pCR with response this combination (45.3%), but there was still a pCR gain of 15% compared with the placebo group (30.3%). The combination of immunotherapy with quite strong chemotherapy in the neoadjuvant setting is therefore beneficial for the patient, whether the tumour is PD-L1 positive or negative.

A large number of combinations have now been tested to try to amplify treatment efficacy. Promising results have been obtained in phase I studies with "triplet" combinations involving a chemotherapy drug, an anti-PD-L1 agent and an Akt pathway inhibitor, with a response rate of 73%, and possibly as high as 82% in the subpopulation of patients who are PD-L1 positive.[20] These results should be confirmed through phase II trials.

Phase II studies are currently testing the use of MEK inhibitors in the early setting, combined with immunotherapy for patients with residual disease after neoadjuvant chemotherapy and presenting with MEK activation. Various combinations of targeted therapies (MEK inhibitors, Akt inhibitors, anti-VEGFs [anti-vascular endothelial growth factor]) and immunotherapies (anti-PD-L1s) are being tested in patients who have either TNBC or residual disease after neoadjuvant chemotherapy, or as first-line treatment in metastatic disease, with or without chemotherapy, in the neoadjuvant situation. These trials should also provide information on the toxicity of these combinations, which may have consequences for patients. The willingness of patients to accept certain toxicities is not the same in early disease as it is in metastatic disease.

Tumour stroma has a greater degree of lymphocyte infiltration (TILs) in patients with TNBC who also have a *BRCA* (breast cancer susceptibility gene) mutation. Poly[ADP-ribose] polymerase (PARP) inhibitors and active cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) stimulate and increase type I interferons. Therefore, the MEDIOLA phase I/II study has evaluated the combination of a PARP inhibitor (olaparib) with immunotherapy (durvalumab) in *BRCA*-mutated patients; the initial results in terms of response rate and duration of response are encouraging.[21]

Epigenetic drugs may also have an important role when used in synergy with other anti-cancer treatments;[22] clinical trials are testing combinations of bromodomain extra-terminal (BET) inhibitors and anti-PD-1/PD-L1s.

Finally, some interesting results have been obtained in a patient with metastatic breast cancer (not triple-negative) with positive chemoresistant hormone receptors, who was treated with TILs reacting to the mutant versions of four proteins (SLC3A2, KIAA0368, CADPS2 and CTSB). The use of these specific TILs in combination with interleukin-2 and immunotherapy (pembrolizumab) resulted in complete long-term remission of this patient's cancer.[23] If this level of efficacy is confirmed across a series of patients, this therapeutic approach could be a route to explore for treatment of patients with TNBC.

It is clear from the above that extensive clinical research is being conducted in the field of TNBC.[24] The results that have been achieved are encouraging in treatment of early stages of the disease, in neoadjuvant treatment and possibly in first-line treatment of metastatic disease. Today, for a patient with TNBC, the priority is to give chemotherapy or a combination of chemotherapy and immunotherapy. Multiple combinations with other immunotherapies and targeted therapies are under evaluation to try to increase treatment efficacy.

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