The Breast xxx (2017) 1–7

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

The emerging world of breast cancer immunotherapy

Mark R. Nathan*, Peter Schmid

St Bartholomew's Hospital, London, UK

ARTICLE INFO

Article history:
Received 21 May 2017
Received in revised form
24 May 2017
Accepted 25 May 2017
Available online xxx

Keywords:
Immunotherapy
Combination therapy
Review
Triple negative breast cancer

ABSTRACT

Over the last few years, the developments around cancer immunotherapy (CIT) have led to a paradigm shift in the treatment of many different cancers, in particular melanoma, renal, bladder and lung cancers with a remarkable impact on response rate and, most importantly, overall survival. Breast cancer is most commonly considered to be a 'non-inflamed' cancer and so this shift has been less marked within its treatment. However, some subsets of breast cancer, most notably triple negative breast cancer, are deemed to be more 'inflamed' and therefore may prove to be an appropriate cohort for CIT.

This review looks back at the theory of the cancer immunity cycle and mechanism of action behind immune checkpoint inhibitors and goes on to explore their role within the various subtypes of breast cancer. It looks at the first trials performed using CIT monotherapy which demonstrated that breast cancer could respond to CIT with a small population reaping considerable benefit. It then examines the continuing body of work being undertaken to explore CIT in combination with chemotherapy to try to increase the proportion of patients who might reap the considerable rewards on offer.

1. Introduction

Over the last few years, the developments around cancer immunotherapy (CIT) have led to a paradigm shift in the treatment of cancer. CIT refers to any treatment that modifies and/or enhances the patient's immune system to fight cancer. Recent studies with CIT have shown unprecedented improvements in survival for a range of cancers, including cancer types that are otherwise relatively refractory to systemic therapy such as melanoma [17,28]. Moreover, many CIT strategies are generally well tolerated without cumulative toxicity and do not share some of the main side effects of conventional systemic cancer therapy. This has resulted in the approval of several new immunotherapy treatments by the FDA and other agencies and the integration of immunotherapy into routine treatments for various cancers. A wide range of CIT strategies is currently undergoing preclinical or clinical investigation and has been extensively reviewed. This review article will primarily concentrate on the current experience with immune checkpoint inhibitors in the treatment of breast cancer.

The ability of the immune system to detect and fight cancer cells is largely based on two key components. Firstly, the immune system has to recognise cancer cells as being "different" from normal cells; the "foreignness" of cancer cells is a critical factor in the immune response and is linked with the expression of neoantigens, which are proteins that are generally not found in normal adult tissues. The occurrence of neoantigens is closely linked with somatic mutations. It is therefore not surprising that a higher mutational load has been linked with an increased benefit from CIT strategies in various cancer types. However, there is increasing evidence that it is not only the number of somatic mutations but also the type of mutations that determines the potential response to CIT.

The second determinant of the immune response is the ability to change the number and function of immune cells when needed. One of the parameters in this context is the extent and the pattern of lymphocytic infiltration of the tumour. In breast cancer, tumour-infiltrating lymphocytes (TILs) have on the one hand been associated with more aggressive-tumour types, but on the other hand have also been linked with improved outcome and response to chemotherapy [2]. TILs have been shown to be an independent prognostic marker in triple-negative breast cancer (TNBC), whereas they are not predictive in ER-positive disease [1,23]. There is also evidence that TILs can be linked with an increased therapeutic response in HER2-positive breast cancer and TNBC [21,29].

However, it is not only the extent and pattern of lymphocytic infiltration, but also the activation status of these immune cells that defines the host's response to tumours. In this complex system, immune checkpoints play a critical role in regulating the immune

* Corresponding author.
E-mail address: mark.nathan@bartshealth.nhs.uk (M.R. Nathan).

http://dx.doi.org/10.1016/j.breast.2017.05.013
0960-9776/

response. Multiple lines of preclinical and clinical evidence have demonstrated that tumours can evade destruction by the immune system by expressing surface ligands that engage inhibitory receptors on tumour-specific T-cells and induce immune tolerance [12,14]. The interaction of PD-1 and PD-L1 seems to play a central role in this process. PD-1 is a member of the immunoglobulin superfamily and acts to inhibit the immune response by inactivating the T cells on which it is expressed, as well as being expressed on B cells, myeloid cells and natural killer cells [4,19]. PD-1 is activated by its ligand PD-L1 that, as well as being expressed by a multitude of immune cells, is expressed on some cancer cells.

The tumour-host interactions are described in the cancer-immunity cycle (Fig. 1) [8]. The first step of this cycle is the release of cancer cell antigens upon the death of cancer cells. This process is referred to as immunogenic cell death. Antigen presenting cells (APCs) such as dendritic cells present these antigens to T cells, resulting in their priming and activation within lymphoid tissues. Cytotoxic T lymphocytes (CTLs) enter the blood stream and migrate to and infiltrate into the tumour microenvironment where they recognise, bind to and ultimately kill the cancer cells [8]. The ultimate aim of immunotherapy is to perpetuate this cycle, causing significant cancer cell death.

There are significant differences between cancer types with regards their pre-existing immunity and their ability to elicit an immune response. Cancers that show a high degree of pre-existing immunity have been described as 'inflamed' cancer types and are characterised by the presence of TILs, PD-L1 positivity of tumours or immune cells, high $CD8^+$ T-cell density or the presence of a strong IFNγ cytolytic T-cell signature [31]. There is increasing clinical evidence suggesting that single agent immune checkpoint inhibitors targeting PD-1/PD-L1 are most effective in these 'inflamed' tumours [3,6]. It therefore follows that patients who do not respond to single agent CIT often exhibit immunosuppressed tumour phenotypes with excluded immune infiltrates or immunologically ignorant immune deserts [9]. Non-inflamed tumours are generally poorly infiltrated by TILs, exhibit low expression of PD-L1 and are characterized by low expression of the antigen presentation machinery [9]. These tumours are incapable of mounting an effective anti-tumour immune response with single agent CIT, but might be converted into an inflamed phenotype through combinations of CIT agents or alongside chemotherapy.

The proportion of breast cancers that could be considered as 'inflamed' tumours is relatively small compared to other disease and varies substantially between subtypes. TNBCs or HER-2 positive breast cancers are more commonly immunogenic than hormone-sensitive breast cancer, as reflected in a higher proportion of TILs [10]. But there are also differences within the group of Hormone-driven breast cancers with Luminal B subtypes being more immunogenic than typical Luminal A tumours.

This review focuses on the role of immune checkpoint inhibition. This is the process by which lymphocyte-inhibitory receptors (eg PD1 and CTLA-4) [15] apply the brakes to the immune system to counter autoimmunity. Cancer cells are able to express the ligands for these receptors (PDL1 and B7 respectively) and thereby dampen down the immune response against them. CTLA-4 antibodies such as ipilimumab block the interaction between CTLA-4 and B7. Likewise antibodies to PD1 (pembrolizumab and nivolumab) and to PD-L1 (atezolizumab and avelumab) inhibit the communication between PD-1 and PD-L1 [25] (Fig. 2). By releasing the brake on the immune system, it is possible to re-invigorate it and allow the T cells to once more identify and kill the cancer cells.

2. Triple negative breast cancer

TNBC is generally considered as the most inflamed breast cancer subtype although there are significant differences between different subgroups of TNBC. New classifications suggest 4 subgroups of TNBC, including two basal-like subgroups that are

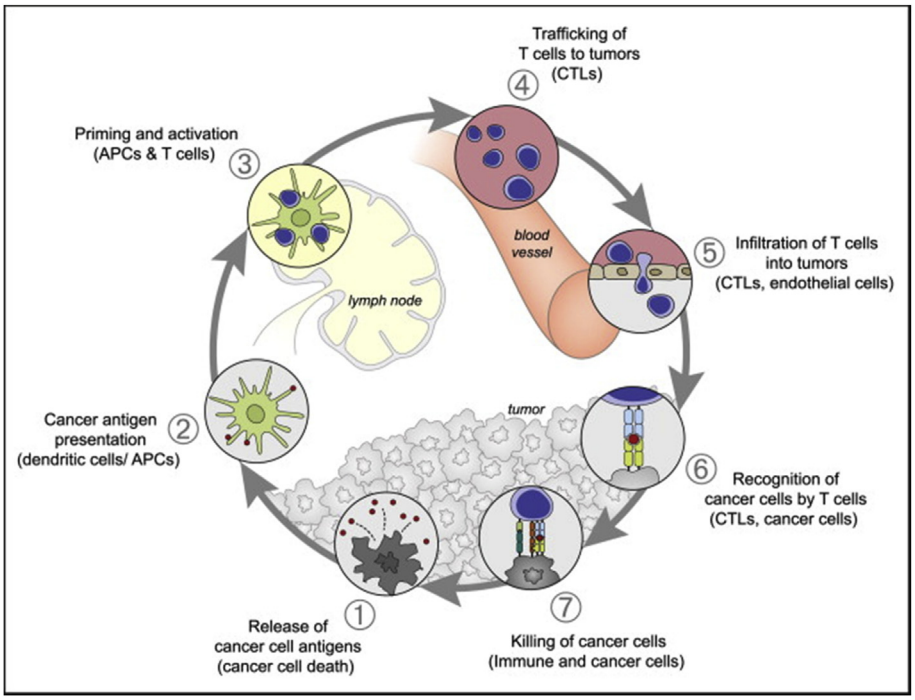

Fig. 1. Cancer immunity cycle. Cancer cell death leads to the release of cancer cell antigens (1). These antigens are the presented on dendritic cells and antigen presenting cells (APCs) (2) which primes T cells (3). Cyctotoxic T lymphocytes (CTLs) then migrate to the tumour (4) and infiltrate it (5). The T cells recognise the cancer cells (6) before killing them (7).

Please cite this article in press as: Nathan MR, Schmid P, The emerging world of breast cancer immunotherapy, The Breast (2017), http://dx.doi.org/10.1016/j.breast.2017.05.013