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Is it time to rethink checkpoint blockade therapy in non-Hodgkin lymphoma?

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Checkpoint blockade therapy (CBT) has revolutionised the management of some malignancies in recent years, leading to long-term remissions, initially with advanced-stage malignant melanoma.[1] More recently, improvements in outcomes have been seen in a wide range of solid tumours including non-small-cell lung cancer (NSCLC) and notably Hodgkin lymphoma.[2,3] In contrast to these practice-changing results, clinical outcomes following CBT in non-Hodgkin lymphoma (NHL) have been disappointing, with overall response rates of ≤10% and median progression-free survival of <2 months with programmed cell death protein 1 (PD-1) blockade in relapsed and refractory diffuse large B-cell lymphoma (DLBCL).[4] This lack of clinically meaningful efficacy has led many haemato-oncologists to conclude that CBT is unlikely to play a significant role in the management of NHL.

Although the reasons underlying the poor clinical responses seen with CBT in NHL are currently far from clear, there are likely to be two broad mechanistic areas underlying these treatment failures. First, due to an inability to induce cognate anti-tumour T-cell responses due to either a lack of recognition of tumour antigenicity or failure of tumour antigen presentation; second, pre-existing anti-tumour immunity may be overcome by suppressive immune effector cells and the cytokine milieu within the tumour microenvironment.

In this issue of the *British Journal of Haematology*, Carreau *et al.*[5] describe the outcomes of treatment beyond failure of CBT for NHL. In a cohort of 60 patients with NHL treated predominantly with agents blocking PD-1 or its ligand, PD-L1, they observe that the duration of response (DOR) for post-CBT therapy was longer than the DOR with preceding lines of treatment, prior to CBT. It is usually assumed that increasing lines of therapy will result in decreasing response rates and DOR. Given that the trend was reversed in this study, with longer DOR to therapy after CBT, the authors argue that CBT may sensitise patients to subsequent treatments.[5] These provocative data are certainly hypothesis-generating and provide an opportunity to re-evaluate how we approach the use CBT in NHL, as a potential 'sensitiser' to chemotherapy, rather than as a single agent in refractory disease.

However, before concluding from this intriguing data that CBT has a clear role in sensitising patients with refractory NHL to further chemotherapy or targeted agents, it is important to outline some of the caveats that undermine the ability to draw firm conclusions. Patients have been selected on account of a lack of durable response to prior therapies, so it is perhaps unsurprising that pre-CBT DOR was short. Furthermore, those patients with the most rapidly progressive disease during CBT may be ineligible for further treatment and absent from this analysis. Patients were also highly heterogeneous in terms of histology and pre/post-CBT treatment. However, the findings in this study of NHL are in agreement with similar retrospective analyses performed in other malignancies, including Hodgkin lymphoma.[6] Encouragingly, they are also supported by preclinical studies demonstrating synergy between selected chemotherapy agents and CBT.[7]

The authors discuss how CBT might interact with the tumour and its microenvironment to enhance the efficacy of subsequent treatments. The ability of many cancer therapies to stimulate anti-tumour immunity has long been recognised, but the extent to which this influences clinical outcomes is underexplored and largely unknown. We know that radiation therapy (RT), doxorubicin and many other agents are able to induce a type of tumour cell death known as immunogenic cell death (ICD).[8,9] ICD results in the generation of an inflammatory environment that activates antigen presenting cells, facilitates leucocyte recruitment and stimulates anti-tumour T-cell responses.[10] Exposure to cytotoxic chemotherapy and RT can also increase expression of stress signals/death ligands and upregulate antigen presentation by tumour cells, facilitating cell-mediated lysis.[11] Other therapies may exert effects directly on the tumour microenvironment,

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by promoting T-cell trafficking and activation, or by suppressing regulatory T cells and other inhibitory elements.[12] CBT lowers the threshold for T-cell activation by neutralising key inhibitory ligands, but cannot induce effective responses against NHL in isolation. The addition of other cancer treatments that induce ICD may provide the additional stimulus required to amplify the anti-tumour immune response to a level that can elicit clinical responses.

The retrospective study by Carreau *et al*.[5] reinvigorates the discussion about the potential role for combining CBT with other therapies in NHL and is of particular interest given that further data are unlikely to be forthcoming, with diminished interest in investigating single-agent CBT in NHL. This study reports on a wide variety of different types of conventional chemotherapy and targeted therapies, so does not provide any insights regarding the preferential ability of any of these treatments to induce ICD over others. Certainly, it is to be expected from experimental data that some treatments, such as doxorubicin, are more able to induce ICD than other chemotherapies.[7] There are also a number of other important clinical considerations, such as chemotherapy dose, that can influence the level of ICD.[12] Corticosteroids and exposure to prior lymphodepleting chemotherapy can suppress the ability to generate robust anti-tumour immune responses. The implications of this are that CBT may be more effective if given at an earlier stage in treatment, when patients may be more able to generate an effective immune response.

There are currently a plethora of trials combining CBT with other chemotherapy agents, testing many different treatment combinations and schedules. However, perhaps the most important issue highlighted by this study is the question of how to schedule CBT relative to chemotherapy. We and others have observed the importance of the scheduling of anti-PD-1 relative to other anti-cancer treatments. In preclinical tumour models, long-term survival was only observed when anti-PD-1 was given before and during RT, but the efficacy being lost when anti-PD-1 was given after RT.[13] The potential importance of this observation is now being extensively investigated in many solid tumours and practice-changing results have already emerged in NSCLC.[3]

Moving forward, a better understanding of the mechanisms underlying CBT failure in DLBCL, together with mechanistic data supporting combination approaches, are needed to inform the design of rational combination therapies. Alongside this, only a more careful and systematic evaluation of the scheduling of CBT relative to chemotherapy will allow us to fully evaluate whether this interesting observation will lead to improved outcome for patients with NHL.

Conflict of interest

Both authors declare no relevant conflicts of interest.

Author contributions

Elizabeth H. Phillips and Tim M. Illidge wrote the article.

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