Commentary

Targeting Neoantigens to Improve Immunotherapeutic Outcome in Medulloblastoma

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In the recently published paper [1] the authors demonstrated a new experimental approach to identify tumour-specific neo-antigens to effectively induce a T-cell specific immune response in paediatric Medulloblastoma in order to improve current/future immunotherapeutic approaches. Paediatric Medulloblastoma is an extremely aggressive embryonal tumour. It is the most prevalent malignant paediatric brain tumour with an incidence rate of about 5 cases per million [2] and is the principal cause of cancer-related death at young age during recurrence/resistance. Immunotherapy has improved overall survival in non-CNS tumours such as paediatric melanoma and leukaemia [3,4]. However, in recurrent/refractory paediatric brain tumours, multiple immunotherapeutic approaches have just entered early phases of clinical trials **(Table 1)** and there is a lack of adequate interim data to correctly estimate toxicity/efficacy so far.

Whether immunotherapy will eventually become a useful therapeutic alternative for patients with paediatric brain cancer depends on multiple factors. Effective eradication of Medulloblastoma during immunotherapy protocols can only be accomplished by overcoming mechanisms adopted by tumour cells to avoid recognition or killing. Different mutational processes in the tumour genome cause tumours to express mutant proteins known as neo-antigens which are tumour specific and not expressed by healthy tissues. These neoantigens can improve immunogenicity and incite an anti-tumour specific immune response against paediatric brain tumours if appropriately presented and recognized by T cells. Higher tumour mutational burden reflects improved neoantigen expression that boosts tumour cell recognition by T cells, leading to enhanced immunotherapy results in melanoma [5]. A recent in-depth analysis of prevalence of somatic mutations across different cancer types showed that Medulloblastoma has extremely low mutational burden which translates to sparse neoantigen production. The identification of tumour-specific mutations is the first crucial step for success of neoantigen-specific T-cell immunotherapies in paediatric brain cancers. Next, T cell mediated tumour killing depends on recognition of antigen and binding of neoepitope on the tumour cell surface by human leukocyte antigen (HLA). However, there are multiple barriers to successfully identifying immunogenic neoantigens:

- Minimal mutational load
- Neoepitope binding affinity prediction and selection
- Tumour heterogeneity
- Mechanisms of resistance such as lack of MHCI expression and mutated neoepitope presentation on tumour surface.

The fresh experimental proof-of-concept strategy introduced by our colleagues to detect immunogenic peptides bears the potential of accurately predicting and validating neo-epitope specific T-cell-mediated immune response in poorly immunogenic tumour such as medulloblastoma in a time span of 10 weeks. This personalized vaccination approach by identifying and delivering patient-specific neo-epitopes within 12 to 14 weeks after sequencing even in tumours with low mutational load opens fresh therapeutic prospects in T-cell specific immunotherapy. However, this strategy heavily relies on the successful presentation of the tumour-specific neo-antigens by MHC-I molecule on the tumour surface. Recent studies have shown that MHC-I expression is completely lost in Group 3 Medulloblastoma lacking functional p53 which could be reversed by low doses of Tumour Necrosis Factor alpha (TNF) *in*

Table 1: Examples of Immunotherapeutic clinical trials listed for paediatric brain cancers including Medulloblastoma.

Trial number	Phase	Recovered from prior radiation and/or chemo	Treatment
NCT03500991	1	Yes	HER2-specific CAR T Cell therapy
NCT03638167	1	Yes	EGFR806-specific CAR T Cell therapy
NCT02271711	1	Yes	Intraventricular infusions of autologous ex vivo-expanded NK Cells
NCT01326104	1,2	No	Dendritic cell vaccine and autologous lymphocyte transfer therapy during hematopoietic recovery from chemotherapy
NCT02457845	1	Yes	Intraventricular injections of HSV G207 Alone or with a single radiation dose
NCT02359565	1	Yes	Pembrolizumab (anti-PD1 antibody)
NCT02457845	1	Yes	Intra-tumoural/-ventricular/-cavitary infusions of IL13Rα2-specific, 41BB-costimulatory CAR/truncated CD19-expressing T cells

vitro [6]. Therefore, in order to harness the absolute potential of current T cell based immunotherapy, it is critical to:

- Identify patient and tumour specific neo-antigen
- Predict and validate neo-epitope specific T cell response
- Examine and if necessary restore MHC-I expression on tumour cell surface
- Assess sustained anti-tumour activity of the neo-antigen-specific response of the T cells using an exhaustive flow cytometric panel.

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