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Review

Challenges and perspectives in the immunotherapy of Hodgkin lymphoma

Jean-Marie Michot [a,b,*], Julien Lazarovici [b], David Ghez [b], Alina Danu [b], Christophe Fermé [b], Amélie Bigorgne [a,c], Vincent Ribrag [a,b], Aurélien Marabelle [a], Sandrine Aspeslagh [a,d]

[a] *Département des Innovations Thérapeutiques et des Essais Précoces, Gustave Roussy, 114 Rue Edouard-Vaillant, F-94805 Villejuif, France*
[b] *Département d'Hématologie, Gustave Roussy, 114 Rue Edouard-Vaillant, F-94805 Villejuif, France*
[c] *INSERM U1163, 24 bd de Montparnasse, F-75015 Paris, France*
[d] *Département d'Oncologie Médicale, Institut Jules Bordet, rue Héger Bordet 1, B-1000 Brussels, Belgium*

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Abstract Hodgkin lymphoma (HL) was one of the first few cancers to be cured first with radiotherapy alone and then with a combination of chemotherapy and radiotherapy. Around 80% of the patients with HL will be cured by first-line therapy. However, the ionising radiation not only produces cytotoxicity but also induces alterations in the microenvironment, and patients often struggle with the long-term consequences of these treatments, such as cardiovascular disorders, lung diseases and secondary malignancies. Hence, it is essential to improve treatments while avoiding delayed side-effects. Immunotherapy is a promising new treatment option for Hodgkin lymphoma, and anti- programmed death-1 (PD1) agents have produced striking results in patients with relapsed or refractory disease. The microenvironment of Hodgkin lymphoma appears to be unique in the field of human disease: the malignant Reed-Sternberg cells only constitute 1% of the cells in the lymphoma, but they are surrounded by an extensive immune infiltrate. Reed-Sternberg cells exhibit 9p24.1/*PD-L1*/*PD-L2* copy number alterations and genetic rearrangements associated with programmed cell death ligand 1/ligand 2 (PD-L1/2) overexpression, together with major histocompatibility complex-I (MHC-I) and major histocompatibility complex-II (MHC-II) downregulation (which may facilitate the tumour's immune evasion). Although HL may be a situation in which defective immune surveillance is restored by anti-PD1 therapy, it challenges our current explanation of

* *Corresponding author*: Département des Innovations Thérapeutiques et des Essais Précoces, Gustave Roussy, 114 Rue Edouard-Vaillant, F-94805 Villejuif, France. Fax: +33 142 116 444.
E-mail address: jean-marie.michot@gustaveroussy.fr (J.-M. Michot).

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how anti-PD1 agents work because MHC-I expression is required for CD8-T-cell-mediated tumour antigen recognition. Here, we review recent attempts to understand the defects in immune recognition in HL and to design an optimal evidence-based treatment for combination with anti-PD1.

1. Introduction

1.1. Sparing the patient from long-term side-effects remains the prime challenge in the first-line treatment of Hodgkin lymphoma

Hodgkin lymphoma (HL) was one of the first few cancers to be cured initially with radiotherapy alone and then with a combination of chemotherapy and radiotherapy [1,2]. Given that HL mainly affects young adults with a life expectancy of over 50 years, the long-term effects of the cancer treatments (such as secondary malignancies, cardiovascular disorders and lung diseases) constitute a major issue [3]. The main delayed-onset toxicities are cardiac disorders (due to exposure to anthracyclines and mediastinal radiation), secondary malignancies (due to radiotherapy and chemotherapy with alkylating agents and etoposide), pulmonary fibrosis (caused by bleomycin) and impaired fertility [4]. Over 25 years of follow-up, the risk of death from the complications of treatment exceeds the risk of death from HL *per se* [5]. To spare patients from these delayed adverse events, the doses of chemotherapy and radiotherapy are tailored as a function of the initial risk factors and the early response after two cycles of chemotherapy [6]. To date, patients with localised HL continue being treated with chemotherapy followed by radiotherapy [7]. The use of modern radiotherapy techniques based on involved-site or involved-node strategies (rather than involved-field strategies) are expected to reduce the incidence of some long-term adverse events [8]. In late-stage HL, the intensive bleomycin/etoposide/adriamycin/cyclophosphamide/oncovin/procarbazine/prednisone (BEACOPP) chemotherapy regimens are associated with an elevated the risk of secondary leukaemia and impaired fertility [4,5].

1.2. After radiotherapy, chemotherapy and molecularly targeted therapies, immunotherapy is becoming the fourth pillar of cancer treatment

In the last 10 years, immune checkpoint blockers have drastically changed cancer treatment. For a long time, cancer was considered to be solely due to the uncontrolled growth of tumour cells, which therefore led to the development of chemotherapy and radiotherapy. From an immunological perspective, the tumour microenvironment has a major role in cancer development [9]. The immune cells are initially activated via danger signals emitted by 'dying', invasive cancer cells and subsequently mount an effective immune response. To circumvent this threat, the cancer cells hijack the immune system so that the immune cells become tolerant allies and do not activate killing by cytotoxic T cells [10]. Tumour inflammation and (in particular) interferon (IFN) gamma production can induce the upregulation of PD-L1 on tumour cells, thereby limiting T-cell cytotoxic activity [11,12]. The revival of immunotherapy in the field of cancer was trigger by the realisation that cancer eradication is prevented by an immunosuppressive tumour microenvironment [13]. Hence, targeting checkpoint inhibitors like programmed death 1 (PD1) (expressed by activated T cells) and its ligand PD-L1 (expressed by both tumour and immune cells) reinvigorates the T-cells' activity against tumour cells [14–16].

2. The Hodgkin Reed-Sternberg cell: a super-specialist in immune escape

2.1. Hodgkin lymphoma has an abundant but inefficient immune microenvironment

Hodgkin lymphoma is characterised histologically by a small number of malignant Hodgkin Reed-Sternberg (HRS) cells. The latter bathe in an abundant polymorphic inflammatory infiltrate that includes T- and B-lymphocytes, macrophages, natural killer (NK) lymphocytes, and eosinophils (Fig. 1). Although HRS cells do not typically express B-cell markers (such as CD19 or CD20), the presence of non-functional immunoglobulin genes that are clonally rearranged and have undergone somatic hypermutation proves that they originate from pre-apoptotic B cells from the germinal centre [17–20]. HRS cells are also characterised by the constitutive activation of two major immune pathways: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway and the signalling cascade involving Janus kinase (JAK)/ Signal Transducer and Activator of Transcription (STAT), i.e. the JAK/STAT pathways. The NF-kB pathway regulates survival of HRS cells through inactivation of mutations of the inhibitory *NFKBIE* gene [21] or by gains or