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Editorial

Novel Strategies to Improve Rituximab Efficacy in Non-Hodgkin's Lymphomas

Editorial

Non-Hodgkin's lymphomas (NHLs) are the second fastest growing cancer in terms of incidence and deaths in the United States and Europe. NHLs are a heterogeneous cancer group including several haematological neoplasias with different degree of aggressiveness. In spite of the progresses, conventional therapies do not ensure long-term survival [1]. The NHL patients, who have a poor life expectation, could take advantage from innovative therapeutic strategies, such as immunotherapy. Specific antibodies can preferentially bind tumour cells over normal tissues. This specificity is based upon characteristics (surface antigens) that are completely independent from the parameters that allow for differential toxicity of chemo- and radiotherapy. The vascular nature of most lymphomas and their antigen expression make these tumours a favourable setting for treatment with monoclonal antibodies. In fact, the first successful use of antibodies as treatments for cancer was demonstrated in NHLs [2,3]. CD20 has been largely exploited as target antigen for immunotherapy with antibodies because it is expressed at high levels on B-lymphoma cells and is not expressed on stem cells [4].

Rituximab is the first mAb approved by US FDA for the treatment of indolent or relapsed NHLs. It is a chimeric antibody, consisting of variable regions of murine origin and constant regions derived from human IgG_1. It is able to kill target cells prevalently by CDC, but also by ADCC and apoptosis [5]. Since its approval in 1997, Rituximab has been evaluated in hundreds clinical trials, not only for lymphoma but also for haematological diseases, either alone or in combination with different agents, such as chemotherapeutics. Indolent NHL patients treated with Rituximab showed a marked increase in survival, as overall response rate (from 79 to 85%), median progression-free survival (from 16 to 33 months) and overall survival (from 84 to 95%) [6]. Today, Rituximab in combination with conventional chemotherapeutics represents the first-line therapy for many NHL types, both indolent and aggressive.

In clinical trials Rituximab is generally well tolerated by NHL patients. The most common adverse reactions observed were infusion-related reactions (fever, lymphopenia, chills, infection, and asthenia) usually mild to moderate, with incidence ≥ 25%. Severe and life-threatening (Grade 3 and 4) events were reported in about 10% of patients, including neutropenia, chills, leukopenia, thrombocytopenia, hypotension, anemia, bronchospasm, urticaria, headache, abdominal pain, and arrhythmia. These adverse reactions were usually reversible with appropriate treatment. Only rare cases of death were reported [7].

Despite the great therapeutic value of Rituximab, many treated patients relapse or become resistant after treatment. Rituximab resistance is due to depletion of complement and effector cells, alteration in complement regulatory protein expression, polymorphisms in FcγRIIIa, selection of neoplastic cells expressing mutated or not expressing CD20 antigen [8]. In order to overtake these limitations different strategies have been exploited.

The first strategy consists in the augment of Rituximab potency and efficacy by the conjugation to a radionuclide [9] or a toxic compound, namely drug [10] or toxin [11]. Immunoconjugates can trigger neoplastic cell death through several pathways and their efficacy only minimally depends on CDC and ADCC. Two Rituximab-based radioimmunoconjugates have been approved by US FDA for treating NHL patients, ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab. Radioimmunoconjugates can kill also cells surrounding the target cells. This characteristic can represent an advantage because they are effective also on cells bearing mutated or lacking CD20 antigen, but also a disadvantage because besides neoplastic cells normal tissues can be damaged too. In clinical trials radioimmunotherapy gave better results than Rituximab in low and intermediate-grade refractory NHLs with an augment in complete responses [12].

A different strategy to improve the results obtained with Rituximab is based on the selection of new engineered anti-CD20 antibodies characterized by reduced immunogenicity and/or enhanced binding affinity for CD20 antigen and for the FcγRIIIa receptor on effector NK cells. A first group of engineered antibodies (also named second generation anti-CD20 mAbs) has been developed with the intent to reduce immunogenicity; it consists of humanised molecules, with murine portion restricted to only hypervariable regions, or fully human molecules (OFA, veltuzumab, and ocrelizumab). A second group (also named third generation anti-CD20 mAbs) consists of engineered antibodies with humanised CDR and modified Fc regions, to augment binding affinity for the FcRIIIa receptor and consequently ADCC (rhumAb v114, ocaratuzumab, obinutuzumab, TRU-015, EMAB-6) [2,4]. Most of these new mAbs are still in clinical trials and several positive results have been reported, despite their complete clinical potential has not been yet exploited.

Certainly, the availability of a panel of human anti-CD20 mAbs

with different efficacy on the various NHL subtypes will lead to an improvement of clinical responses.

This scenario indicates that a future golden age for NHL therapy can be near when it will be possible to match the more effective and tolerated agents with a single lymphoma subtype, obtaining personalized schedule tailored to single lymphoma patients.

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