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 surrounding the target cells. This characteristic can represent an advantage because they are effective also on cells bearing mutated or not expressing CD20 antigen [8]. In order to overtake these limitations different strategies have been exploited.

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 overcome 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, 90Y-ibritumomab tiuxetan and 131I-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) has been developed with the intent to augment binding affinity for the FcγRIIIa 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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References

7. Product Information. Rituxan (rituximab).” Genentech, South San Francisco, CA.