Antisense oligonucleotide targeting Bcl-2 messenger RNA in cancer: bad drug, bad target, neither or both?

We have read with a great interest the letter entitled “Targeting bcl-2 protein in treatment of melanoma still requires further clarifications” by Pisano et al. [1]. In this letter, the authors suggested that oblimersen, an antisense oligonucleotide (ASO) targeting Bcl-2 messenger RNA, may induce a Bcl-2-independent cellular apoptosis in seven melanoma cell lines. To support this conclusion, the authors observed that oblimersen induced a more important cell growth reduction in Bcl-2-negative cell line than in an appropriate control. At the same time, oblimersen demonstrated the poorest antiproliferative effect in the Bcl-2-expressing cell line. We think that this conclusion requires some comments to avoid a misleading message.

First, the authors have not used an appropriate control to assess the specific effect of the anti-Bcl-2 oligonucleotide. Some studies have reported that oblimersen exhibited immunostimulatory properties [2], and appropriate controls, such as reverse oligonucleotide or antisense mismatch control, are mandatory to blind this nonspecific class effect. Secondly, the concentration used in this publication is a lot higher than the concentrations used in previous publications [3]. The authors used a 250 μM concentration; whereas other studies have shown that oblimersen effectively down-regulates Bcl-2 expression at concentrations below 1 μM. This high concentration increases the likelihood of nonspecific effect.

Thirdly, the authors provided no information about Bcl-2 expression in cells treated with oblimersen. Additional data are required to demonstrate that oblimersen effectively down-regulates Bcl-2 expression and finally induces apoptosis in the selected cell lines [4]. Finally, oblimersen may have a greater antitumoral effect in combination with other treatments. Some studies have shown that apoptosis-modulating agents are more efficient in association with chemotherapy or radiotherapy than alone [5].

Hence, we agree with the authors that targeting a single component within the multiple signaling pathways involved in the biology of cancer, and in particular in apoptosis, is unlikely to induce significant antitumor responses. However, preclinical evaluation of molecular targeted therapies should address the following aspects in order to answer the question of efficacy:

1. Does the ASO get into the cells? (cellular uptake)
2. Is the ASO effective at down-regulating the target? (pharmacodynamic criteria)
3. Is the activation of the target a prerequisite for the efficacy of the drugs?

We do agree that the oligonucleotide approach may not be optimal, but the main pitfall is probably an insufficient tumor penetration, rather than hypothetic nonspecific side-effects. Our conviction is that oblimersen may have provided better clinical results if patients had been selected for Bcl-2 over-expression. Pharmacological Bcl-2/Bcl-xl dual inhibitors are more attractive but these drugs will also fail if reasons for the failure of oligonucleotides are not clearly depicted.

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References


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