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LETTER TO THE EDITOR

Cetuximab-dependent ADCC in cancer: dream or reality?

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Dear editors,

Monoclonal antibodies (MoAb) offer one of the most interesting therapeutic approaches in patients with advanced cancer. Cetuximab is a chimeric IgG1 monoclonal antibody that binds to the epidermal growth factor receptor (EGFR) with a tenfold higher affinity than its natural ligands [1] and prevents ligand-induced phosphorylation of the intracellular tyrosine kinase (TK) domain and activation of the signaling cascade. Preclinical studies indicated that cetuximab inhibits proliferation, metastasis and angiogenesis in human cancer models [2]. In first line metastatic colorectal cancer (mCRC) treatment, cetuximab adds substantial benefit to standard oxaliplatin- and irinotecan-based combinations and in second line treatment it might restore sensitivity to irinotecan [3]. Cetuximab in combination with radiotherapy is also effective in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [4] and, in combination with platinum-based chemotherapy, for recurrent and/or metastatic disease [5]. Recent evidence shows that mCRC responds differently to EGFR-targeted agents depending on the genetic basis, so that oncogenic activation of EGFR downstream effectors (i.e., KRAS, BRAF, PIK3CA and PTEN) influences the response to EGFR-targeted therapy [1].

The mechanism of action of cetuximab is not completely understood. However, an antibody-dependent cell-mediated cytotoxicity (ADCC) has been suggested [1, 2]. ADCC is induced through the interaction of the Fc region of the MoAb with the Fc gamma receptor (FcγR) expressed by effector lymphocytes [e.g., natural killer lymphocytes (NK cells, monocytes/macrophages)] and is regulated by a complex balance of inhibitory and activating signals including membrane co-receptors and serum proteins (cytokines, chemokines and hormones). Recently, it has been shown that FcγR polymorphisms may have a predictive role for the outcomes in mCRC patients treated with cetuximab [6]. In the manuscript by López-Albaitero et al. [7], it is reported that NK cells derived from patients with SCCHN are the lytic effector cells in the cetuximab-dependent response and that the expression of an FcγR IIIa-158 V allele on their surface strongly correlates with ADCC activity, NK cell activation, degranulation and secretion of several cytokines with anti-tumor activity (e.g., IFN-γ, TNF-α, MIP-1α, MIP-1β). Interestingly, in the presence of high-level EGFR expression, cetuximab-mediated lysis of SCCHN cell lines by NK cells expressing the poorly binding FcγR IIIa FF (FF-NK cells) allele was barely detectable, suggesting that the Fc genotype markedly affects the cetuximab response even more than the EGF-R expression. The authors also investigated the possibility of improving the response to cetuximab of subjects with FF-NK cells by specific cytokines. Of note for clinical applications, FF-NK cells treated with IL-2 or IL-15 achieved an equivalent activation status, measured by expression of the specific activation markers CD69 and CD107α, as NK cells expressing the higher affinity FcγR

Please note that we are simultaneously publishing a letter by Ottaiano et al., which is a response to the paper by López-Albaitero et al., published in 2009 (Cancer Immunol Immunother 58:1853–1862), and a response by Ferris and Ferrone to the Ottaiano letter.

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IIIa-158 V allele. This resulted in increased cetuximab-mediated lysis of tumor cells.

This study clearly showed that specific FcγR IIIa-158 genotypes affect cetuximab-dependent cellular cytotoxicity and underlines the importance of a correct evaluation of the individual patient's immunological status. However, although ADCC induction appeared convincing in "in vitro" models, some concerns could be raised in cetuximab-treated cancer patients. First of all, the conventional association of cetuximab with chemotherapy minimizes the possibility of an efficient immune response in patients with limited number and activity of lymphocytes. In fact, it was shown that ADCC was strongly impaired in cancer patients because of NK cell dysfunction [8], and often NK and T cell functions are impaired due to reduced number, imbalances in their activating and inhibitory receptor repertoire, as well as the multifactorial cancer patient immunosuppressive environment [9].

The design of clinical studies on MoAb-based anticancer therapy requires the prospective evaluation of the functional status of NK and T cells, as well as of regulatory cell subsets (Treg, MDSC, B-Reg, Th17) and peripheral cytochemokines (CCL4, CCL5, IL-17, IL-21, CXCL12, IFN-γ, TNF-α, MIP-1α, MIP-1β, etc.). Once again, a multidisciplinary approach (medical oncology, immunology, molecular biology, biostatistics, etc.) is needed to optimize the cancer patient's treatment.

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