Editorial

Dulanermin in cancer therapy: still much to do

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Cancer therapy is the challenging goal of the new millennium. Since traditional chemotherapy induces cell death through the activation of p53-mediated intrinsic apoptotic pathway, most tumours bearing p53 mutations result totally or partially resistant to therapy. This condition could be overcome through the activation of the extrinsic apoptotic pathway (1). Apo2L/TNF-related apoptosis inducing ligand (TRAIL) is the best characterized molecule belonging to this pathway (2). From the observation that TRAIL is able to trigger apoptosis selectively in cancer cells and not in normal cells, it has been considered a good therapeutic candidate in cancer. Another interesting characteristic of TRAIL-induced apoptosis is the total independence of p53 activity (3). This propriety can be useful in the treatment of all forms of tumors resistant to the traditional chemotherapy. TRAIL is a member of TNF ligand superfamily, and triggers apoptosis by binding with high affinity to two receptors, DR4 (TR-1, TNFRSF10A) and DR5 (TR-2 TNFRSF10B). This binding recruits adaptor proteins and induces the formation of the death inducing signalling complex (DISC) leading to the induction of apoptosis. Several studies indicate that APO2L/TRAIL has an anti-tumor activity both in vivo and in vitro in a wide varieties of cancer cell lines including colon, lung, glioblastoma (4). Despite the initial enthusiasm, different reports suggest that not all cancer cells respond to TRAIL. TRAIL resistance may be due to different factors, included different expression levels of pro and anti-apoptotic proteins within a cells or of microRNAs able to target proteins involved in TRAIL pathway (5-10). In this case it has been observed that the combination of TRAIL to traditional chemotherapy or radiotherapy may overcame the resistant phenotype. Due to all indicated properties, proapoptotic receptor agonists (PARAs) able to activate the extrinsic apoptotic pathway, have been developed. Between them in clinical development there are monoclonal antibodies able to bind DR4 and DR5 and a human recombinant form of Apo2L/ TRAIL, dulanermin. Recently, a study published in *Journal of Clinical Oncology* (11) reports a randomized phase II study which attempts to demonstrate the antitumor activity of dulanermin in combination with standard therapy [paclitaxel, carboplatin (PC) and bevacizumab (PCB)] in advanced non small cells lung cancer (NSCLC). In this study, within 213 enrolled patients with advanced NSCLC (squamous and non squamous), 120 received dularemin in combination with PC or PCB. As in phase I study, also in this study dulanermin was shown to be well tolerated with not toxicity or adverse effects on patients (12). However, the combination of dulanermin to traditional chemotherapy did not seem to significantly increase antitumoral activity neither in association with PC nor with PCB. This data are in contrast with previous clinical trials that suggest that dulanermin is able to explicate an anti-tumoral effect on untreated, advanced non squamous NSCLS (12) and chondrosarcoma (13). The message of this new clinical trial is clear: dulanermin doesn't improve the response of advanced NSCLC patients to conventional chemotherapy. However, some question remain unsolved. Dulanermin works binding DR4 and DR5 (3) but in these trials the expression of receptor has not been deeply investigated. It is possible that in advanced stages of NSCLC the expression of both receptors could change. Alternatively, other mechanisms of tumor-resistance have been developed in cancer advanced state. It is possible that clinical trials conducted in patients at early stages of the tumor, may give more objective responses. Another point that has to be defined, is the possibility of

using circulating markers for the follow-up of dulanermin response. Identifying a predictive biomarker that is able to distinguish between responder and not responder is important to the successful clinical development of a drug. As other reports, this study indicates an increase of serum cleaved cytokeratin-18 and immunoistochemestry positivity of GalNT14 upon dulanermin administration (12,14,15). However, it is not evident the association of these markers with changes in tumor progression. It is not clear if the increase of those markers is associated with an increase of apoptosis in tumor cells or in other cells. Moreover, a small population of samples have been analyzed. In conclusion, this as well as other clinical trials on PARAs inhibitors have not at the moment given an objective response on the usefulness of TRAIL-based therapies. Due to the importance of activation of apoptotic pathway for cancer therapy, future researches are needed: (I) to give insights into the mechanisms of resistance; (II) to identify patients that most likely may benefit of such therapies; (III) to understand molecular factors that might limit the response.

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