

> TARGETED THERAPIES IN CANCER: MYTH OR REALITY?

From empiricism to molecular targeted therapies

Background

ONCOLOGY RESEARCH: FROM EMPIRICISM TO MOLECULAR TARGETED THERAPIES

The recent identification of oncogenetic processes at a molecular level has constituted an historical turning point in the development of innovative cancer therapies, allowing scientists and clinicians to set their therapeutic aims higher than ever before: to identify targeted drugs capable of selectively blocking tumour growth without producing a negative effect on the patient's quality of life.

Cancer is destined to become an increasingly chronic condition, thus the availability of diversified forms of treatment which are wider-reaching and more articulated than those of the old generation, is required. To this regard, particularly heterogeneous treatment options aimed at destroying cancer cells by means of various mechanisms which may or not be used in conjunction with traditional antiproliferative therapies based on the use of cytotoxic drugs are currently undergoing development. Targeted therapies have come to represent not only the reference standard for those involved in cancer research but, for several forms of the disease, are already in use as a consolidated therapeutic means.

Although both strive to reach the same aim – to check growth of the cancer-, traditional forms of treatment and targeted therapies diverge as to the rationale and procedures by means of which they are developed. This is not merely a technical issue but rather a matter of facing the cancer question from a completely new perspective. Targeted therapies have led to a veritable “Copernican revolution” in the field of oncology, passing from empiricism to the identification of molecular cancer targets.

Empiric methods were applied in the past in the discovery of “traditional” cancer drugs identified on the basis of their capability to inhibit growth of cancer cells “in vitro” and “in vivo”. The mechanism of action of these compounds was only investigated *a posteriori*, subsequent to their discovery, by performing a series of more detailed studies.

Drugs discovered by empiric means, the traditional cytotoxic agents still in use today in protocols of chemotherapy, are characterised by a low selectivity for cancer cells. Indeed, their action is directed towards all cells in the body displaying a high proliferation – cells of the bone marrow, skin, oral and gastrointestinal mucosa – thereby determining the manifestation

of a large number of important side effects such as nausea, vomiting, immunodepression, alopecia etc... which still today severely affect the quality of life of the patient.

Moreover, with regard to the therapeutic aim, it is unlikely that the empiric approach will prove capable of targeting the molecule underlying the transformation into cancer cells. Treatment therefore will produce a scarcely specific action on the mechanisms of oncogenesis.

On the contrary, in “targeted therapies”, also known as “target-centric” treatments, the objective to be reached is identified *a priori*, being constituted by the altered molecular process within the cancer cell. As already well known, cancers are manifested following molecular deficits causing cells to proliferate in the absence of external stimuli, to elude apoptosis, to avoid control by the immune system, form new blood vessels and invade healthy tissues.

The transformation of cells into cancer cells is based on the presence of genetic mutations which have been manifested in one’s lifetime or, more rarely, inherited, capable of determining an altered qualitative or quantitative synthesis of several proteins. Numerous types of cancer are affected by the same molecular alterations. The new generation “target-centric” therapies act at the level of these alterations.

The mechanism of action of the latter agents represents the starting point for research processes. The target concerned is established *a priori* on the basis of molecular biology studies and the discovery of new drugs is supported by avant-garde technologies affording extremely high levels of efficacy.

The “target-centric” paradigm is widely accepted throughout the world and today represents the standard approach in the search for new anti-cancer drugs.