Combining molecular targeted therapeutics (MTT) and radiotherapy: MTT and MTD

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Combining radiotherapy with molecular targeted therapeutics (MTT) has had a direct impact on standard therapy after the publication of a report on the combination of cetuximab and radiotherapy in head and neck cancer that demonstrated improved overall survival and local control. To date, a substantial number of MTT have become available and a significant number of drugs targeting novel molecules are in the pipeline. The combination of MTT with radiotherapy is likely to be very important because radiotherapy is used in more than 50% of all cancer patients and therefore combining MTT with radiotherapy may benefit the majority of cancer patients.

The evolution of our knowledge of the mechanisms of action of radiotherapy in the patient has taken the following major steps. In the past we have learned to use clinical factors such as tumour size, stage and target coverage to explain failure. Then, we learned that intrinsic radioresistance, repopulation and hypoxia are three major biological factors affecting outcome. Lately, technical progress in the form of IMRT/IGRT and particle therapy, for example, has permitted normal tissue injury to be reduced and radiation dose to be escalated to increase the chance of local control alone, but these effects have been dramatically increased when combined with MTT. The latest step has been the introduction of MTT into radiotherapy to streamline and individualise therapy similar to a tailor fitting clothes to a customer according to his or her individual features.

The use of MTT started as single-agent therapy in the traditional way, such as was previously done with chemotherapeutic agents. However, it has become clear that most monotherapies are unlikely to lead to cures or long-lasting responses because of the genetic plasticity of tumour cell populations. Simultaneous treatment with two or more agents that have very different mechanisms of action diminishes the probability of acquired resistance in an exponential way: radiotherapy can typically reduce tumour cell burden to several decades lower compared with chemotherapy and is therefore especially promising when combined with a molecular targeted agent to achieve local control.

In addition to this, some of the candidate drugs are only truly powerful mechanistically when they are used in combination with others. It is highly likely that many useful drug candidates have been discarded in the past because they have never been tested in the right combinations. However, our increasing understanding of the signalling circuitry within tumour cells will probably allow us to better understand these relationships to exploit them therapeutically. Radiation biologists are especially interested in deciphering molecular pathways mediating resistance to radiotherapy in order to develop rational treatments for the respective subtypes of cancer. The major target groups are discussed below:

The modulation of DNA repair has taken a central place for a long time to enhance the effects of radiotherapy because DNA damage is crucial for survival after ionising radiation. Since tumours, in contrast to normal tissue, are often defective in specific aspects of DNA repair their back-up pathways can be targeted for radiosensitisation. Such approaches may exploit the proliferative nature of tumours: e.g. PARPi (poly ADP-ribose polymerase inhibitors), which are currently being tested in early clinical trials inhibit base-excision repair (BER) and single-strand break repair (SSBR). This leads to additional formation of DSB because unrepaired SSB are converted to DSB during replication. The use of PARPi is specifically promising in patients with defects in DNA repair, such as *BRCA1* and *BRCA2*, as blocking the back-up SSBR pathway will lead to synthetic lethality.

In close relation to DSB repair, cell cycle checkpoint modulation is another strategy that can be used to selectively target tumour cells for sensitisation to radiotherapy. Almost all tumour cells have faulty G1/S phase checkpoint activation by mutations of p53 or other factors in the p53 pathway. These cells depend more on the function of the G2 checkpoint and this Achilles' heel can be targeted by drugs such as Chk1 and Chk2 or ATM inhibitors. As a consequence the tumours will have less repair time and therefore have enhanced cell kill after radiation compared with normal tissues.

A number of signal transduction pathways have been identified that impact on survival after radiotherapy: the four most important of these are the EGFR-Ras-PI3K-Akt pathway, the MAPK pathway, the NF-κB pathway and the TGFβ pathway, which are all frequently activated in cancer and therefore inhibitors (specific antibodies and kinase inhibitors) have been developed. The most prominent example is the EGFR-specific antibody cetuximab, which was tested together with radiotherapy in a randomised phase III trial in head and neck cancer, and increased survival and local control. All of the above-mentioned pathways have been linked to effects on DNA repair and additionally inhibitors of the EGFR-Ras-PI3K-Akt pathway were found to increase perfusion and to reduce hypoxia, a major biological factor of radioresistance.

Another major biological aspect influencing response to radiotherapy is the modulation of the microenvironment. Hypoxia and vasculature development are the two main investigated features in this context. Oxygen concentrations below 0.02% make tumour cells more resistant to killing by radiotherapy by a factor of 2 to 3. This results in a difference of several logs of cell killing between hypoxic and normoxic cells. Several ways have been investigated to tackle hypoxia:

(1) Increasing blood oxygen by breathing higher oxygen concentrations
(2) Specific radiosensitisation of hypoxic cells with electron affinic drugs, which mimic oxygen (e.g. nimorazole)
(3) The use of compounds that kill hypoxic cells more efficiently than normoxic cells (e.g. tirapazamine)
(4) More recently the use of signal transduction inhibitors in the EGFR-Ras-PI3K-Akt cascade improving perfusion and reducing hypoxia over several weeks
(5) The targeting of angiogenesis (e.g. VEGF) and of vasculogenesis where blood vessels are formed from circulating bone marrow-derived cells (BMDC) has also been investigated to increase tumour responses after radiotherapy.

Whereas the previous paragraph summarised the promising breadth of targeted approaches enhancing radiotherapy, this section is about the introduction of these drugs for clinical use. Classically, new agents have been introduced into oncology using the key concept of the maximum tolerated dose (MTD) paradigm. This has to do with the steep dose-response curves and poor efficacy of standard chemotherapy in patients with terminal illness. Typically, these drugs have narrow therapeutic windows and a poor selectivity of action on cancer cells leading to the conclusion of "the more, the better". But even before the introduction of targeted agents this concept was proven to be false, for example, when high-dose chemotherapy administered with autologous stem cell support in diseases such as metastatic breast cancer. The development of targeted therapeutics aiming to selectively inhibit a key pathway led to the development of new paradigms aiming for "optimal biological dose" (OBD). This is based on the observation that maximum inhibition of a target can often be achieved at exposure levels that generate minimal or no toxicities in normal tissues. For instance, monoclonal antibody therapies may have no MTD because they do not have any dose-limiting toxicities at pharmacologically achievable concentrations. Nevertheless, we are aware of toxicities at clinically relevant doses for some of our best known targeted therapeutics: imatinib has gastrointestinal toxicities, erlotinib and other EGFR tyrosine kinase inhibitors cause severe skin reactions and bevacizumab is known to induce hypertension. Therefore, classical dose escalation phase I studies have not become entirely irrelevant, but, in contrast to chemotherapy phase I studies, the result of such a dose escalation is different. The MTD no longer allows deduction of the recommended phase II dose (RPTD); rather, it is necessary to collect biomarker data alongside early phase trials in order to detect reasons for efficacy and failure of the novel compound at testing. The integration of the results of phase I trials and biomarker analysis might even lead to recommending a randomised phase II trial dosing the new compound at various dose levels. Gefitinib and temsirolimus were FDA-approved at the lower doses in randomised phase II trials.

In conclusion, the progress of the past decades has allowed us to understand much better the biological background of the effects of radiotherapy. A number of MTTs that have been tested in the clinic demonstrated dramatic efficacy with and without radiotherapy. At the same time many preclinical observations combining MTTs with radiation support our hopes of being able to introduce more combinations of this kind into radiotherapeutic approaches. Using novel early phase clinical trial strategies integrating biomarker studies, this could lead to dramatic increases in local tumour control.

Conflict of interest statement

The authors have no conflicts of interest to disclose.