Review Article

New challenge of developing combined radio-drug therapy

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Abstract: Combined modality treatment can be used to improve control of the local disease at the expense of increased toxicity. Several randomized trials have demonstrated that this combined modality therapy is better than radiotherapy alone or chemotherapy alone in the treatment of locally advanced diseases. Several new targets as well as potential new radio-sensitizers have been identified. To speed-up the process of developing new combined modality treatments, good preclinical models for optimization of the ratio between efficacy and toxicity and a well established methodology within a network of advanced high-tech laboratories and clinical departments devoted to early phase trials, are mandatory. The Synergy of Targeted Agents and Radiation Therapy (STAR) platform of the European Organisation for Research and Treatment of Cancer (EORTC) is gathering these tools.

Keywords: Radiotherapy; chemo-radiation; early phase trials; radiobiology; targeted agents

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Introduction

Radiation therapy (RT) is one of the three therapeutic pillars among cancer treatment regimens. Numerous approaches have been tested to improve the therapeutic ratio of RT, and these include increasing the dose delivered to the tumor, altered fractionation schemes, combined modality treatment with chemotherapy, and, more recently, novel targeted agents (1). This last approach is based on a mechanistic understanding suggesting that a combined approach with RT could enhance the killing of tumor cells through inhibition of DNA repair processes and the inhibition of tumor repopulation between RT fractions.

Combined modality treatment can be used to improve control of the local disease at the expense of increased toxicity. Several randomized trials have demonstrated that this combined modality therapy is better than RT alone or chemotherapy alone in the treatment of locally advanced cancer of the head and neck (HNC), lung, esophagus, and rectum, as well as high grade glioma. Following the introduction of 5-fluorouracil (5-FU) associated with RT in advanced HNC in the early 1980's, different combinations using classical cytotoxic agents have been studied (2).

The Radiation Oncology Group (ROG) of the European Organisation for Research and Treatment of Cancer (EORTC), formally known as the Radiotherapy Group, has conducted more than 80 clinical trials, three quarters of which have been randomized phase III trials. The ROG has played a major role in changing clinical practice having shown the impact on outcome of combined chemo-RT in the pre-operative treatment of locally advanced rectal cancer (3), of the combination of temozolomide and RT in glioblastoma (4), and of chemo-RT in the post-operative setting of HNC (5). It did so for locally advanced prostate carcinoma with the combination of hormonal and radiation therapies (6). Furthermore, this success story has been associated with a dramatic improvement in quality of life of patients receiving chemo-radiation for advanced laryngeal

carcinoma in voice preservation trials as well as for rectal and anal cancer in sphincter preservation trials (7-14).

Rationale

The first trial to use a monoclonal antibody (MoAb) was one in which patients with HNC were treated with cetuximab combined with RT. This phase III trial comparing RT alone to concomitant treatment with RT and cetuximab showed that the outcome of patients receiving RT in combination with this chimeric MoAb directed against the epidermal growth factor receptor (EGFR) is improved compared to patients who underwent RT alone (15). Furthermore, this molecule has been proven efficacious in locally advanced or metastatic HNC in combination with 5-FU and cisplatin (16). Preclinical and clinical studies have demonstrated the efficacy of cetuximab in combination with RT. However, increased skin toxicity, mainly acneiform rash, has been reported underlining the need for better early assessment of potential toxicity in various preclinical models. In a comparison between RT combined with platinum based chemotherapy versus RT with cetuximab, a significantly higher number of grade 3 oral mucositis and dermatitis were observed in the cetuximab containing arm; this must be outweighed by the higher risk of hematological toxicity by cisplatin based radio-chemotherapy. So far, these adverse events have been reported only for HNCs; in trials on thoracic or pelvic RT with cetuximab, increased rates of skin toxicity have not been observed. Unfortunately, following this preliminary experience, other antibodies combined with RT have shown neither an increased rate of local tumor control nor an increase in overall survival as compared to radio-chemotherapy. Panitumumab, a MoAb directed against EGFR, has a higher affinity and fewer hypersensitivity reactions due to its non-chimeric character, but it failed to demonstrate a significant therapeutic impact when combined with RT (17). Similar results have been obtained with nimotuzumab (18).

There are many factors that determine tumor cell sensitivity to radiation. Three important biological processes have been shown to affect tumor response and outcome after RT: hypoxia, the ability of the surviving cells to repopulate during the course of treatment, and the intrinsic radio-resistance of the tumor cells. In addition, micro-environmental host factors such as tumor infiltration of inflammatory cells and other bone marrow-derived cells (BMDCs) have been shown to play a role. A complementary approach associated with the development and the implementation of new technologies is to contribute to the reduction of normal tissue injury induced by ionizing radiation. This is especially important in dose escalation studies, when the aim is to increase the probability of tumor control. Both approaches, increasing tumor cell kill and decreasing morbidity, even in the context of combined modality treatment, can improve cure rates and quality of life of cancer patients undergoing RT.

It is obvious that the development of a combined modality strategy is of key importance for about half of the patients suffering from cancer, considering that local control of the primary tumor should first be obtained. RT is the main actor along with surgery for this goal. Therefore, the traditional research on RT focusing on improving technical delivery has to be associated with improvement in combined modality treatment to optimize the acute tolerance and late toxicity of associated treatments on normal tissues.

Combining novel targeted approaches with radiation therapy (RT)

Several processes have been identified as potential targets for radio-sensitization, and perhaps the most famous one is modulating DNA repair (19). Owing to genetic instability, tumors are often defective in one aspect of DNA repair, but usually have backup pathways for accomplishing repair. Attacking these backup pathways can render the tumor radio-sensitive while leaving the normal tissue relatively resistant. Since tumors are often defective in one of the cell cycle checkpoints (such as the G1/S checkpoint), the modulating of cell cycle checkpoints is another important potential approach. Inhibiting remaining checkpoints can leave tumors with less repair time, resulting in greater cell kill than in normal tissues. The PI3K-AKT, nuclear factor-κB (NF-κB), MAPK pathways and others can mediate radio-resistance and are often aberrantly activated in tumors. Attacking these pathways with specific inhibitors of signal transduction is a promising avenue for increasing the radio-sensitivity of tumors (20).

More recently, efforts have been made to better understand the role of the microenvironment: tumors often contain radio-resistant and chemo-resistant hypoxic cells. Several methods are available to attack or exploit tumor hypoxia, leading to tumor-specific effects. Tumor vasculature can also be attacked in ways that increase the response to ionizing radiation. Moreover, a variety of strategies for modulating normal tissue damage has shown promise in ameliorating ionizing radiation

damage to normal tissues. These include protection with radical scavengers, stimulating recovery with cytokines, modifying the p53 response, reducing the negative effects of inflammatory cascades and oxidative stress, and stem cell therapy.

Radio-sensitization

DNA damage response (DDR)

DNA damage induced by ionizing radiation triggers the DDR which comprises molecular events that mostly involve post-translational modification of proteins that activate intracellular signaling pathways. Repair of double strand breaks (DSBs) requires arrest of cell cycle progression to avoid further damage before commitment to S-phase or mitosis. Oncogene-driven DNA replication stress has been implicated as a cause of constitutive activation of DDR and tumor progression. Defects in both DNA repair and checkpoint responses in tumor cells affect the response to ionizing radiation and can be exploited for targeted radio-sensitization strategies. Inhibitors of important molecules in DSB repair, such as ataxia telangiectasia mutated protein (ATM) or DNA-dependent protein kinase (DNA-PK), have been shown to sensitize cancer cells and xenografted tumors to RT. New agents have been developed in recent years and tested in phases I, II, and III trials concomitantly with RT or chemo-RT to sensitize cancer cells and xenografted tumors to RT. One class of such drugs, the poly (ADP-ribose) polymerase (PARP) inhibitors, has shown activity in conjunction with RT in several cancer cell lines (21). Clinical trials assessing the toxicity and potential benefit of combining RT with PARP inhibition are now ongoing.

Cell cycle checkpoints

Besides DNA repair, cell cycle checkpoints constitute another important component of DDR. Induction of DNA damage by ionizing radiation in normal cells halts their progression through the cell cycle and prevents further accumulation of damage and its serious consequences. In contrast, in cancer cells with an impaired G1 checkpoint, cell cycle progression will continue unabated, and therefore removing the G2 block will increase damage and its transmission to progeny (22). This will ultimately lead to the loss of clonogenicity, and this is the rationale of checkpoint inhibition strategies. ATM and downstream proteins such as the cell division cycle 25 (CDC25) phosphatase represent cell cycle checkpoints in response to ionizing radiation that would otherwise prevent the propagation of DNA damage. CDC25 phosphatase and ATM inhibitors have been used as single agents but have also been demonstrated to enhance cell kill in combination with DNA-damaging drugs and RT.

Signal transduction pathways: the EGFR-PI3K-AKT axis

The importance of PI3K-AKT as a survival pathway has led to the development of a multitude of blocking antibodies and small-molecule inhibitors. The most successful to date is the EGFR-specific antibody cetuximab, which in combination with RT significantly increased local-regional tumor control and overall survival in a phase III trial in HNC. Receptor tyrosine kinase inhibitors (TKIs) can also abrogate the EGFR signaling cascade, and this leads to increased radio-sensitivity. In some preclinical models, antibodies seem to be more effective at modifying the ionizing radiation response than TKIs. Four pathways demonstrate a clear role in the response and sensitivity to ionizing RT: PI3K-AKT, nuclear NF-κB, MAPK, and TGFβ. The activation of AKT by phosphorylation occurs through growth factor receptor pathways, e.g., receptor overexpression such as EGFR, loss of PTEN, oncogenic mutations in NRAS or KRAS, all of which have been shown to be associated with increased resistance to RT in tumor cell lines. EGFR-directed MoAbs and TKIs most likely increase radio-sensitivity by inhibiting DNA repair.

Histone deacetylase (HDAC) inhibitors

HDAC-I acts predominantly by inducing differentiation, apoptosis, and cell cycle arrest with a preferential cytotoxicity for tumor cells (apoptosis induction). HDAC-I induces cell death (via an unclear mechanism involving mitochondrial apoptosis, autophagy, regulation of reactive oxygen species, etc.) and cell cycle arrest mainly in G1 but also demonstrates anti-angiogenic, anti-invasive, and immune-modulatory activities (23). The exact mechanism by which HDAC inhibitor-induced radio-sensitization occurs is currently unclear, but may be, at least in part, due to the preventing the repair of damaged DNA. Thus, HDAC inhibitors appear to inhibit DNA double strand breaks (DSB) repair leading to enhanced tumor cell death. Radio-sensitization has also been explained by modulation of cell cycle regulation and down-regulation of surviving signals. One of the major advantages of HDAC inhibitors as radio-sensitizing agents for cancer therapy is the fact

that they are relatively specific for malignant cells and spare normal tissues. Several *in vitro* studies have demonstrated this finding of no increased radio-sensitivity in normal tissue cell lines when exposed to HDAC inhibitors, and some HDACs may actually play a role in protecting normal tissue from radiation-induced side effects (inhibition of TNF-α and TGF-β). Even though cutaneous T-cell lymphoma (CTCL) is the only cancer for which HDAC inhibitors are currently FDA-approved, many clinical trials are assessing the efficacy and safety of other HDAC inhibitors when used alone or in combination therapies in both solid and hematologic malignancies. Clinical trials, in conjunction with new insights from basic scientific research, will help elucidate which treatment combinations and dosing regimens are optimal for various types of cancers in the context of varied patient characteristics and biomarker profiles.

Heat shock protein 90 (HSP90) inhibitors

Hsp90, a 90 kDa heat shock protein, is a highly expressed molecular chaperone that mediates maturation and activation of client proteins, and plays a critical role in establishing resistance to RT. Among Hsp90 clients are a number of proteins which contribute in a cell type-dependent manner to tumor cell radio-resistance. Exposure of a variety of solid tumor cell lines to clinically relevant Hsp90 inhibitors results in tumor growth suppression and increased induction of therapeutic cell death. Whereas an increase in radio-sensitivity of tumor cells was consistently reported, the radio-sensitivity of normal fibroblasts was not affected by Hsp90 inhibition. This suggests that there might be a potential for tumor-selective radio-sensitization. The molecular chaperone Hsp90 has been the focus of a number of investigations as a multi-target approach to radio-sensitization. The Hsp90 inhibitors evaluated to date enhance the *in vitro* radio-sensitivities of cell lines initiated from prostate and lung tumors (24,25).

Hypoxia/angiogenesis: modulating the microenvironment

Both, hypoxia and vascularization, can exert a considerable influence on the response to ionizing radiation, and both are rewarding processes to intervene for improving the response to therapy. Hypoxia leads to the activation of the hypoxia-inducible factor (HIF) and unfolded protein response (UPR) pathways, both of which determine survival under this stress. High expression of hypoxia-inducible genes is often associated with poor prognosis. More continuous exposure can lead to down-regulation of the DNA repair gene RAD51 and others as well as an increase sensitivity to crosslinking agents. A recent systematic review of published and unpublished data identified 4,805 patients with HNC undergoing curative intended primary RT alone. These data from 32 randomized clinical trials were analyzed with regard to the following endpoints: loco-regional control (32 trials), disease specific survival (30 trials), overall survival (29 trials), distant metastases (12 trials) and complications to RT (23 trials). Overall, hypoxic modification of RT in HNC resulted in a significantly increased therapeutic benefit (26).

The problem of hypoxia can be tackled in several ways. The first is to increase blood oxygen. Oxygen delivery can be increased by using drugs such as efaproxiral which reduce oxygen-hemoglobin binding. Using a different approach, Ogawa *et al*. (27) developed a radio-sensitizing treatment that directly oxygenated the tumor by intratumoral administration of hydrogen peroxide and sodium hyaluronate. Second, many oxygen-mimetic/electron-affinic drugs have been developed that specifically radio-sensitize hypoxic, but not normoxic cells. Several drugs underwent clinical testing, but only the 5-nitroimadazole nimorazole showed efficacy in phase III trials. A randomized phase III trial will test the added value of this drug to cisplatin combined with RT in an EORTC trial dedicated to locally advanced human papilloma virus (HPV) negative HNC. The third is by mimicking the redox systems of nitroimidazoles, and fourth, the chemistry of transition metal complexes has been exploited for use in radio-sensitization, the best example of which is cisplatin. Fifth, hypoxic cytotoxins have been developed that kill hypoxic cells with far greater efficiency than normoxic cells. This is an alternative to radio-sensitizing hypoxic cells, and modelling studies indicate that it is the more effective strategy to combine with RT. Tirapazamine is the archetypical drug, although it did not show efficacy in a recent phase III trial in combination with RT and cisplatin. But, we are well aware of the impact that compliance by the centers to the RT protocol can have on the results of a randomized phase III trial dedicated to locally advanced HNC (28). Poor compliance jeopardized the outcome and created a demonstrated bias in the final analysis of the trial.

Hypoxia-induced up-regulation of HIF1α leads to angiogenesis through the up-regulation of vascular endothelial growth factor A (VEGFA) and other growth factors. In addition, vasculogenesis (vascular formation from circulating BMDCs) has been shown to be crucial

for the growth of tumors that recur after RT. VEGF is the key pro-angiogenic growth factor that is secreted by almost all solid tumors and acts through VEGFR1, VEGFR2 or VEGFR3 receptors on endothelial cells. Vasculogenesis also depends on hypoxia, which is more extensive in recurrent tumors and leads to up-regulation of cytokines which in turn recruit and activate the BMDCs necessary for vascularization. In preclinical models, inhibiting vasculogenesis by various interventions, both genetic and pharmacological, dramatically increases tumor responses after RT and was more effective than inhibiting angiogenesis. This represents a fairly new and promising way to increase the response to RT.

Apoptosis modulation

Modulation of apoptosis sensitivity, mainly linked to caspase activation, has emerged as a promising strategy to increase radiation-induced cell kill and improve clinical outcome. There are two major pathways for the activation of inducer caspases: the mitochondrial-dependent intrinsic pathway and the extrinsic pathway involving ligand-binding death receptors at the cell surface. Most apoptotic stimuli, including radiation and chemotherapy, depend on the intrinsic mitochondrial pathway in which induced permeability of the mitochondrial outer membrane permits the release of pro-apoptotic factors into the cytosol. The activation of the extrinsic pathway depends on ligand binding to cell surface death receptors, such as tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors and CD95 which are members of the TNF receptor superfamily and activate inducer caspases at the death domain in their cytoplasmic tail (29). Interventional strategies that target apoptotic pathways can be distinguished as those that promote pro-apoptotic signaling and those that inhibit anti-apoptotic signaling. While of interest as a therapeutic modality in itself, TRAIL is also an excellent candidate for combination therapy, since TRAIL and radiation activate partially distinct apoptosis signaling pathways, and a molecular basis for synergy may lie in the up-regulation or sensitization of the TRAIL receptor complex by radiation.

Prerequisite for the development of novel combined radio-molecularly targeted agents

To speed-up the process of developing new combined modality treatments, good preclinical models for optimization of the ratio between efficacy and toxicity and a well established methodology gathering quality controls within a network of advanced high-tech laboratories and clinical departments devoted to early phase trials, as well as trained in implementing new imaging modalities including fluorodeoxyglucose (FDG)-positron emission tomography (PET) and new tracers, useful for monitoring or predicting response to RT, are indispensable (30). Even if it has been well demonstrated that FDG PET is useful to study the glucose metabolism of tumor cells, proliferation could be studied by fluorothymidine (FLT)-PET and hypoxia by fluoromisonidazole (F-miso) and fluoroazomycin arabinoside (FAZA) (31). Receptor-based imaging has also been introduced with tracers targeting EGFR, HER2 and the somatostatin receptor. Efficacy induced by RT combined with chemotherapeutics or targeted agents induce changes in a tumor's physiology, metabolism and proliferation which often precede volumetric changes. Therefore, reliable biomarkers and imaging modalities that could assess treatment response more rapidly or even predict tumor response to treatment at an early phase, would be very useful in identifying the responders and/or avoiding toxic therapies in non-responders. The currently available assays to detect the most prominent types of radiation induced cell death (apoptosis, necrosis, mitotic catastrophy, autophagy and senescence) *in vitro* and *in vivo*, have been described comprehensively by Verheij (32).

In the framework of the EORTC, a strategic initiative called Synergy of Targeted Agents and Radiation Therapy (STAR), offers industry and pharmaceutical companies an efficient and robust preclinical evaluation of the combination of new molecular targeted therapy and RT. The duration of phase I RT combination studies is perceived as a major challenge by the pharmaceutical industry (33), and there is a lack of acceptable endpoints for such RT studies and of defined regulatory pathways to consecutive approval. In order to convince the pharmaceutical industry of a dedicated drug development program, the EORTC ROG is providing a network of experienced radiotherapy departments, a radiation therapy quality assurance (RTQA) program dedicated to clinical trials, disease oriented group working parties, strong connections with the EORTC Imaging and Pathobiology Groups, and working in close connection with a headquarter platform. It could facilitate the rational selection of agents and provide a straightforward methodology for conducting early clinical trials. In the future, multi-study agreements between pharmaceutical companies with such academic and independent clinical trial groups should be favored so as to

incorporate pre-clinical research into agreements for drug development.

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