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Radiotherapy and targeted therapy – a review of the literature

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Radiotherapy (RT) is an important treatment modality for cancer treatment patients. Approximately 50% of all cancer patients receive RT during the course of their illness. A great potential to improve treatment results involves combination RT with other methods. The combination of RT and cytotoxic chemotherapy is a clinically well-established and documented method to improve survival. Integration of targeted therapy with RT may provide therapeutic benefit by exploiting biologic and genetic differences between cancer and normal tissues while minimizing additional toxicity. The aim of this paper is to present a literature review of the effectiveness of combination radiotherapy and molecular targeted therapy.

Key words: radiotherapy, targeted therapy, monoclonal antibodies, small-particle drugs

Introduction

Radiotherapy (RT) is an important treatment modality for cancer treatment patients. Approximately 50% of all cancer patients receive RT during their course of illness [1]. The mechanism of RT is based on the interaction of ionising radiation with matter (biological material – tissue of body). The consequence of this interaction is the deposition energy of ionizing radiation in the cells of tissues it passes through. An important biological result of RT is DNA damage which may arise directly through the ionization atoms that make up DNA molecules, or indirectly, through generating free radicals. These processes cause double-stranded or single-stranded breaks of DNA, which lead to cell death and failure of mitosis. Therefore, ionizing radiation induces DNA damage and disrupts cell cycle progression, resulting in impeding cell division and blocking proliferation [2–6].

The main goal of RT is depriving cancer cells of proliferation and the killing off of these cells. There are a variety of mechanisms for killing cancer cells by RT:

- mitotic death (or mitotic catastrophe) – which occurs during or after aberrant mitosis and cell death due to chromosome missegregation during mitosis [7–9],
- apoptosis – programmed cell death, the major mechanism of cell death which is involved in cancer therapy, RT particular [10–12],
- necrosis – the process when a cell visibly swells with the breakdown of cell membrane, this mechanism is seen less frequently after RT [13],
- senescence – permanent loss of cell proliferative capacity, this mechanism occurs in cancer cells following extensive stress (RT-induced also) and later cells die by a process of apoptosis [14, 15],
- autophagy is a form of cancer cell death in response to radiotherapy, it is a genetically regulated form of programmed cell deaths [5, 16].

Because radiation damages both cancer and normal cells, the goal of RT is to maximize of dose to the tumour while minimizing exposure to normal cells which are adjacent to

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the cancer or in the path of the radiation) [17]. Through the advanced technologies used in the delivery of RT, it is possible to administer maximum RT dose to the tumor whilst sparing normal tissues. Moreover, precision delivery of RT enables dose escalation [2].

The biological effectiveness of RT (cell killing) depends on factors such as linear energy transfer, fractionation rate and the radio-sensitivity of targeted cells, and is a result of processes occurring within the cells [2, 18, 19]:

- repair of sublethal damage,
- reassortment of cells in the cycle,
- repopulation of cells during the course of RT,
- reoxygenation of hypoxic cells.

Consideration of the above factors is the rationale for the application of modified dose fractionation regimens [2, 5]. Another possibility to improve treatment results refers to combination RT with other methods. The combination of RT and cytotoxic chemotherapy is a clinically well-established and documented method to improve survival [20]. Integration of targeted therapy with RT may provide therapeutic benefit by exploiting biologic and genetic differences between cancer and normal tissues while minimizing additional toxicity [4].

Rapid development of molecular targeted therapy enabled the improvement of the results of cancer therapy by combining targeted therapies with RT [21]. Targeted therapy is connected with the concept of individually tailored treatment because it is effective in patients whose cancers have a specific molecular target [5, 22]. Targeted therapy involves drugs that block proliferation of cancer cells, or induce apoptosis.

Targeted therapy uses monoclonal antibodies or small-particle drugs. Monoclonal antibodies block a specific target in cancer cells, and they are used with chemo- and/or radiotherapy. Whereas small molecules inhibitors interrupt the cellular process by interfering with intracellular signalling of tyrosine kinases (which initiate molecular cascade to cell growth, proliferation, migration, angiogenesis) [2].

The pathways targeted in cancer therapy can be inhibited at multiple levels by binding ligands to the specific site of a receptor, by occupying receptor-binding sites preventing ligand binding, by blocking receptor signalling or by interfering with downstream intracellular molecules [2, 22].

The aim of this paper is to present a literature review of the effectiveness of combining radiotherapy and molecular targeted therapy.

EGFR inhibitors

At present, cetuximab (EGFR inhibitor) is the only molecularly targeted drug registered in Europe and the US in combination with RT in head and neck cancer patients. In the Bonner et al. trial [23], patients were randomly assigned to receive either radiotherapy alone or radiotherapy with cetuximab. Radiotherapy plus cetuximab proved to be more effective in terms of overall survival (OS): 49 *vs.* 29.3 months, 5- year OS: 45.6% *vs.* 36.4%. Combination therapy also contributed to a significant prolongation of progression-free survival (PFS) without significant effect on the toxicity of treatment (except for infusion reactions and a cetuximab-specific rash). The Bonner et al. trial proved the efficacy of cetuximab combined with radiotherapy, however, it should be noted that there was no arm with cisplatin in this study. Two large trials (De-Escalate [24] and RTOG 1016 [25]) proved the superiority of cisplatin–RT over cetuximab–RT. The De-Escalate study showed similar toxicity in both arms with significantly higher efficacy of cisplatin–RT (2-year OS: 89.4% *vs*. 97.5% respectively). In the RTOG 1016 trial, cetuximab also failed to meet the assumed non-inferiority criterion with similar early- and long-term toxicity of treatment. Moreover, despite encouraging results in head and neck cancer patients, cetuximab has not demonstrated an effective radiosensitizing effect in other cancers where the EGFR pathway is an important therapeutic target.

Erlotinib, an oral inhibitor of EGFR tyrosine kinase, was studied in combination with radiotherapy and temozolomide in patients with EGFR-overexpressed glioblastoma multiforme. Despite the theoretical assumptions for the effectiveness of such a combination, the phase II studies demonstrated contrasting results, however, with the overall tendency to increase the toxicity of treatment without the obvious survival benefit. Among patients with pancreatic cancer, erlotinib has also not demonstrated sufficient efficacy in combination with radiotherapy (both as an adjuvant treatment or for locally advanced, non-restrictive disease [26–30]).

Everolimus, an mTOR inhibitor (another molecule downstream of the EGFR/PI3K pathway) also did not demonstrate sufficient efficacy in combination with radiotherapy. In phase II studies in glioblastoma multiforme patients, NCCTG N057K [31] and RTOG 0913 [32] showed no improvement in survival and increased toxicity.

Radiosensitizing molecules targeting hypoxic tumor cells

Nimorazole (molecule targeting hypoxic tumor cells) proved to be relatively effective as a radiosensitizer. In the phase III trial, a 16% improvement in the locoregional control of cancer of the supraglottic larynx and pharynx was achieved, compared to radiotherapy alone [33]. At present, except for Denmark, this drug is not adopted as a standard of care.

In two large phase II clinical trials, promising results of the ARCON molecule (in combination with radiotherapy in head and neck and bladder cancer patients) were achieved. As a result, phase III studies were conducted – BCON [34] and Janssens et al. [35], in which the effectiveness of ARCON in patients with bladder cancer and laryngeal cancer, respectively, was studied. In the case of bladder cancer patients, the combination of ARCON and radiotherapy proved to be more effective in terms of OS and local control than radiotherapy alone. In patients with laryngeal cancer, the effective-

ness of the drug was proven only in patients with hypoxemic tumors. Finally, given the inconclusive results of the phase III studies, the difficulty in delivering the drug and the identification of patients with highly hypoxemic tumors, the drug did not gain widespread acceptance.

Clinical trials of tirapazamine – another hypoxia-oriented radiosensitizing molecule [36] – also failed. There were no improved outcomes both in cervical and head and neck cancer patients when tirapazamine was combined with chemoradiation compared to conventional chemoradiation alone.

Drugs targeting DNA damage response mechanisms

The phase I study evaluated the efficacy of veliparb (PARP inhibitor) with concurrent radiotherapy in patients with inflammatory or recurrent breast cancer [37]. Despite acceptable overall treatment toxicity (only five – 16.7% – patients experienced a dose limiting toxicity), nearly half of surviving patients experienced G3 adverse events at 3 years. Half of the patients experienced disease control failure and 43% died after 3 years of follow-up. Considering these results, a long-term follow-up seems to be essential in trials of radiosensitizing drugs. In another phase I study, veliparb was studied in combination with radiochemotherapy in locally advanced homology recombination repair deficient pancreatic cancer patients [38]. The median OS was 15 months. Currently, a phase II study comparing radiotherapy with or without olaparib (another PARP inhibitor) is ongoing in patients with inflammatory breast cancer. Olaparib has also been studied in combination with cetuximab and radiotherapy in squamous cell head and neck cancer patients with a long-term tobacco history [39]. This combination turned out to be safe, with a 2-year OS of 72%, which is better than in historical studies without olaparib (60%).

Adavosertib, a WEE1 inhibitor, has recently been studied in a phase I study with radiotherapy and gemcitabine in 34 patients with locally advanced pancreatic cancer [40]. The median OS was 21.7 months, which is much more than in previous studies evaluating radiotherapy with gemcitabine. Another promising molecule is peposertib (DNA-PKC inhibitor), phase I studies with this drug are currently ongoing.

Nanotechnology

NBTXR3 is the first in its class radiosensitizer (hafnium oxide nanoparticle). In the phase II/III trial, a significantly higher percentage of total pathological responses was obtained in patients whose soft tissue sarcomas were injected with NBTXR3 prior to radiotherapy. No significant increase in treatment toxicity was observed between the groups [41]. The main problem in this type of treatment is the delivery of the drug to the tumor.

Conclusions

The dynamic development of targeted drugs in oncology inevitably involves attempts to use these drugs in combination with radiation therapy. Despite the theoretical preconditions for the effectiveness of such a procedure, cetuximab is currently the only widely registered targeted drug used with radiotherapy. Despite its lower efficacy than classical radiochemotherapy, the use of cetuximab is associated with lower toxicity than standard chemotherapy, which is particularly important for patients with contraindications to cisplatin. In the case of other molecules, phase III studies often did not show their superiority over the current standard of care. Another problem is how the drug is delivered to cancer cells, in the case of a route of administration other than intravenous or oral, even with the promising efficacy of a given molecule, it is unlikely that it will be widely used in everyday practice.

At the moment the greatest hope of success, in combining targeted therapies with radiotherapy, seems to be drugs targeted at mechanisms of DNA repair. A major challenge in the case of modern, extremely expensive drugs will be finding the right predictive factors so that as many patients as possible benefit from the treatment.

Conflict of interest: none declared

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