VIA MEDICA

Radiotherapy in the combined treatment

NOWOTWORY Journal of Oncology
2022, volume 72, number 5, 319–325
DOI: 10.5603/NJO.2022.0051

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Combined radiotherapy and chemotherapy

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Combined radiotherapy and chemotherapy is a standard procedure in radical treatment of many cancers. The objective of chemoradiotherapy is to increase loco-regional control, to reduce the risk of distant metastases and to prolong survival, and thus to improve treatment efficiency with less mutilating therapies. Concurrent chemoradiotherapy, however, is more toxic than chemotherapy and radiotherapy alone or sequential application of these methods. Optimalisation of combined treatment requires further research. New possibilities arise with inclusion of targeted treatment and immunotherapy in classical chemoradiotherapy.

Key words: radiotherapy, chemotherapy, combined treatment

Historically, the first method of treating neoplasms was surgery. Inclusion of radiation in neoplasm therapies allowed combination of those two methods. For several decades, radiotherapy supplementing surgery affected improvement of loco-regional control. Unfortunately, a range of factors specific for the tumour itself and for the patient limited efficiency of surgery alone, radiotherapy alone, and combination of the two methods as well. Among these factors, one should list impossibility to remove excessive tissue volumes and inability to deliver the high radiation dose to the target area due to the threat of permanent damage to healthy tissues. Inability of efficient anti-cancer therapy using only local treatment methods is also associated with infiltration of surrounding tissues beyond outside the primary tumour, metastases to distant organs and micro-metastases. The concept of multi-modal oncological treatment including systemic treatment created a chance to surpass the limitations involved in surgery and radiotherapy.

Currently, combination of radiotherapy and chemotherapy is a standard procedure in radical treatment of many cancers [1–3]. The objective of chemoradiotherapy is to increase loco-regional control, to reduce the risk of distant metastases and to prolong survival, and thus to improve treatment efficiency. It is assumed that combination of these methods makes the treatment less mutilating, allowing for preservation of organs and their functions [4, 5].

Chemoradiotherapy was applied for the first time in the early 1950s. The first cytostatic agent used in combination with radiotherapy was 5-fluorouracil [6]. Before the end of the 1950s, 5-fluorouracil was successfully implemented in combination with radiotherapy in treatment of gastrointestinal cancers, cervical cancers and head and neck cancers [7].

Originally, it was believed that radiotherapy and chemotherapy are interdependent in terms of efficiency and toxicity. The theoretical background for combining radiotherapy and chemotherapy was developed in 1979 by Steel and Peckham [8]. They described four potential ways how combined therapy might improve the therapeutic index, now known as Steel Paradigm:

- spatial cooperation,
- toxicity independence,
- better protection of normal tissues,
- enhancement of tumour response [4, 5, 8].

How to cite:

Rucińska M. ***Combined radiotherapy and chemotherapy.*** *NOWOTWORY J Oncol* 2022; 72: 319–325.

Spatial cooperation

The concept of spatial cooperation assumes that radiotherapy and chemotherapy act entirely independently from each other. Radiotherapy acts loco-regionally, destroying the primary neoplastic tumour, while the systemic therapy is mainly focused on destroying micro-metastases. According to the concept of spatial cooperation, no interaction between chemotherapy and radiotherapy is needed – radiotherapy has local effect and chemotherapy acts on disease outside a radiation field and these effects accumulate. This approach to benefits of chemoradiotherapy can be illustrated with sequential chemotherapy and radiotherapy in breast cancer, as well as prophylactic brain radiation after completing chemotherapy in small-cell lung cancer.

Toxicity independence

Originally Steel and Peckham [8] assumed that as toxicity of cytostatic agents and radiation do not overlap, it would possible to kill cancer cells without enhancement of the toxic effect to healthy tissue. The concept of spatial cooperation provided exactly for independent toxicity of radiotherapy and chemotherapy, enabling relevant protection of healthy tissues and enhanced response to treatment with concurrent application of the two methods. However, this was not achieved in clinical practice. It was shown that concurrent introduction of chemotherapy and radiotherapy increases side effects of the anticancer therapy. In fakct toxicity adds up and moreover radiation can cause chemosensitisation or chemotherapy can cause radiosensitisation [4]. The standard of practice is to avoid direct overlap of toxicity of cytostatic agents and radiotherapy (e.g. methotrexate with radiation to the brain or bleomycin with radiation to lungs).

Protection of normal tissues

Another concept associated with combining chemotherapy and radiotherapy, as proposed by Steel and Peckham [8] involved a process targeted at protection of healthy tissues from adverse effects of radiation (radioprotective properties). However, no chemical substances have been identified that would protect normal tissues from adverse effects of radiotherapy, thus affecting the therapeutic index. A limited success was achieved with amifostine – it was only shown to reduce the risk of xerostomia after radiotherapy of the head and neck cancers [9].

Enhancement of tumour response

It seems that an important role in combination of chemotherapy and radiotherapy is radiation sensitisation effect of some cytostatic agents, which increases local efficiency of radiation. Better loco-regional control concurrent with systemic effect of cytostatic effects may also reduce the potential to metastasise. Radiosensitising effect of chemotherapy with respect to radiotherapy suggests enhanced efficiency in the case of concurrent application of the two methods as compared to their sequential use [4, 5].

Through the ionisation mechanism, radiotherapy causes directly or indirectly physical and chemical changes in the cell – mainly in its DNA. Theoretically, radiation sensitisation can be achieved by a range of interactions:

- direct increase of cell sensitivity to radiotherapy by damaging DNA,
- inhibiting accelerated repopulation,
- inhibiting cell repair,
- accumulation of cells in the radio-sensitive phase, or
- elimination of cells in the radio-resistant phase,
- improvement of cell oxidation [4, 5, 10–12].

Damaging DNA

Radiobiological principle of "radiosensitiser" provided that a drug would enhance post-radiation DNA damage. If a drug particle connects to DNA of a cancer cell or causes DNA damage itself, it increases DNA sensitivity to damage caused by radiation. Such drugs include 5-fluorouracil and cisplatin.

Inhibiting accelerated repopulation

When there is a partial cell loss caused by radiation, other cancer cells respond with accelerated repopulation. Cytotoxic or even cytostatic drugs have anti-proliferation effect and concurrently with radiation they may prevent accelerated repopulation of cancer cells between each radiotherapy fractions. This increases the tumour's sensitivity to radiation, and thus increasing chances for local recovery [13].

Inhibiting damage repair

Cancer cells which can effectively repair DNA damage display significant resistance to radiation. This is why compounds which interrupt transduction of the DNA damage repair signal may exacerbate the toxic effect of irradiation by inhibiting repair of sub-lethal and potentially lethal damages. Some chemotherapeutical agents disturb biosynthesis of nucleotides – for example 5-fluorouracil, gemcitabine, methotrexate, etoposide, cisplatin. Further, compounds which intervene in cell cycle may inhibit DNA repair indirectly.

Affecting cell distribution in the cell cycle

The highest sensitivity to radiation is recorded in cells in the G2 and M phases of the cell cycle and the lowest – in the S phase. A range of chemotherapeutical agents are phase-specific. Radiation efficiency is increased by compounds which may accumulate cells in radiation-sensitive phases and those which may eliminate cells from radiation-resistant phases. Taxanes and nucleoside analogues, as well as modified pyrimidines seem to have exactly this effect [14, 15].

Improvement of cell oxidation

Solid tumours contain areas of lower-oxidation cells. Hypoxia reduces efficiency of radiotherapy, as its effect relies mainly

on generating free radicals. This is why drugs which reduce hypoxia may increase efficiency of radiation. Through cytotoxic effect, chemotherapy may simply reduce tumour size, thus reducing parenchymal pressure and making oxygen flow into cells easier. Further, with the death of quickly proliferating cells, hypoxic cells get closer to vessels [16]. Additionaly, such drugs as nitroimidazole compounds may imitate / replace oxygen in hypoxic areas, reducing the negative effects of hypoxia [17].

Different sensitivity to treatment of different cell clones

A never concept explaining the benefits of chemoradiotherapy assumes that radiotherapy and chemotherapy kill various cell clones independently from each other [13]. With the heterogenous nature of cancers, some neoplastic cells are resistant to radiation, but they may prove to be sensitive toconcurrent administered chemical compound. An example of such cooperation may be found in application of hypoxic cytotoxins, e.g. tirapazamine in combined therapy of the head and neck cancers.

The cytotoxic agents improving effectiveness of radiotherapy

Antimetabolites

5-fluorouracil affects cell distribution in the cell cycle, influencing cells in the S phase of the cell cycle, which are radiation resistant. It also causes re-oxygenation of hypoxic cells [12, 15, 18]. Administration of 5-fluorouracil during radiotherapy by continous infusion or orally is more efficient than in bolus [19].

Alkylating drugs

Mitomycin C inhibits DNA and RNA synthesis by interrupting cross bonds, mainly at guanine and cytosine pairs. Although mitomycin C is not cell cycle-specific, it arrests cells in the G2/M phase of the cycle. In combination with radiation, mitomycin C acts as radiosensitiser for cells in hypoxia and prevents repopulation [20–23].

Temozolomide damages DNA by DNA methylation in the position of 0-6 guanine. The methylation triggers the abnormal DNA repair pathvay, leading to increased cell sensitivity to irradiotion and leads them to the apoptosis [24, 25]. Additionaly temozolomide inhibits repopulation of cancer cells [12, 18].

Platinum-base drugs

Cisplatin consolidates DNA damages induced by irradiation – potentially repairable changes (e.g. interruption of the DNA strand) become lethal damage. It inhibits DNA synthesis and transcription, inhibiting repair of post-radiation damage to DNA [12, 26–28]. Cisplatin acts both in well oxidated and hypoxic cells [29]. Meanwhile, radiation facilitates cisplatin penetration into cancer cells and formation of its active metabolites [30–32].

Drugs affecting microtubules of the spindle apparatus

Vinca alkaloids affect the cell cycle itself – they cause depolymerisation of microtubules and interrupt functioning of the mitotic spindle. This results in arresting cells in the radiotherapy-sensitive M phase. They also inhibit repair of radiotherapy-induced DNA damage [33].

Taxanes stabilise microtubules, thus inhibiting centrosomes, which leads to deceleration of mitosis and cumulation of cells in G2 and M phases of the cell cycle [12, 33–35]. Taxanes reduce parenchymal pressure and thus allow better oxidation of cancer cells, making them more sensitive to irradiation [12, 16, 34]. Taxanes induce apoptosis [12, 35].

Topoisomerase inhibitors

Etoposide and topotecan inhibit repair of post-radiation DNA damage, they arrest cells in G2 phase, process single breaks of DNA strands into double ones [12, 36, 37].

Examples of application of chemoradiotherapy

There are various ways to combine chemotherapy with radiotherapy. Chemotherapy can be applied as neoadjuvant or adjuvant therapy, as sequential / alternating with radiotherapy or concurrent with radioteherapy.

Anal cancer

In the 1970s for the first time it was showed that anal cancer can be cured effectively with chemoradiotherapy applying 5-fluorouracil and mitomycin C without a surgical treatment [38]. Two out of three patients treated with 5-fluorouracil, mitomycin C and radiation achieved full pathologic response and progression-free survival was 14 months [38]. These results were confirmed in further studies [39–42]. The EORTC phase III study showed that chemoradiotherapy with 5-fluorouracil and mitomycin C provides better local control and longer colostomy-free survival as compared to radiotherapy alone [40]. The reduction of risk of death related to the anal cancer and prolongation of overall survival (7.6 *vs.* 5.4 years) was observed [43]. Patients who received 5-fluorouracil and mitomycin C significantly less frequently underwent colostomy, and 4-year progression-free survival in this group is higher as compared to patients treated with 5-fluorouracil only (73% and 51%, respectively) [44]. Concurrent chemoradiotherapy based on 5-fluorouracil and mitomycin C is currently considered standard management of the anal cancer. Modern radiotherapy techniques allow reduction of toxicity, but they do not contribute to improvement of overall survival [45].

Rectal cancer

Four big trials indicated that addition of chemotherapy to the preoperative radiotherapy in the rectal cancer in stage II and III, increases the rate of complete responses and improve

local control [46–50]. Preoperative chemoradiotherapy was shown to be more effective than post-operative chemoradiotherapy with respect to local control and sphincter preservation. This aproche was less toxic than adjuvant treatment [51]. Neoadjuvant chemoradiotherapy is nowadays a standard in treatment of locally advanced rectal cancer.

Oesophageal cancer

The RTOG study (85–01) showed that radiotherapy combined with chemotherapy (5-fluorouracil and cisplatin) improved significantly the five-year overall survival (26% *vs.* 0%) [52, 53]. This was also confirmed by newer studies [54, 55] and a meta-analysis [56]. Preoperative chemoradiotherapy affects improved results of the surgical treatment. The CALGB 9781 study showed that patients treated with neoadjuvant chemoradiotherapy had significantly better prognosis (median overall survival of 54 *vs.* 21.6 months; 5-year overall survival of 39% *vs.* 16%) [57]. Similar findings were recorded in the study published by van Hagen et al. (median overall survival of 49.4 *vs.* 24 months; 5-year overall survival of 47% *vs.* 34%) [58]. Preoperative chemoradiotherapy contributed to significant reduction of the locoregional recurrence as compared to surgery only (from 34% to 14%) [59]. The current standard of treatment of the locally advanced oesophageal cancer is surgery preceded by chemoradiotherapy or chemoradiotherapy alone(cisplatin with docetaxel or paclitaxel).

Cervical cancer

A large randomised trial found that cisplatin-based chemoradiotherapy improved disease-free survival as compared to neoadjuvant chemotherapy followed by a radical surgery (77% *vs.* 69%) [60]. Many randomised studies showed better rate of disease-free survival and overall survival with chemoradiotherapy as compared to radiotherapy alone in locally advanced cervical cancer [61–64]. For the locally advanced cervical cancer chemoradiotherapy has become a standard treatment. Currently, the following is seen as the most promising scheme: neoadjuvant chemotherapy (carboplatin / paclitaxel) and then chemoradiotherapy [65, 66]. Although it has been found that chemoradiotherapy is associated with significantly higher risk of toxicity to the rectum, urinary bladder and vagina three months after the treatment, after two years the risk was not higer (with the exception of vaginal toxicity) [60].

Non-small cell lung cancer

Three big randomised trials published in the 1990s showed improvement in treatment results of locally advanced non-small cell lung cancer with application of sequential chemotherapy and radiotherapy [67–69]. With sequential chemoradiotherapy, an increase of five-year overall survival was recorded from 5% to 10% [67, 70, 71]. Auperin et al. showed in 2010 [72] that five-year overall survival of patients with non-small cell lung cancer treated with concurrent chemoradiotherapy is almost 5% higher that with sequential treatment, reaching 15%. Concurrent therapy is associated with a high risk of oesophageal toxicity and pneumonia. Currently, standard treatment of the locally advanced inoperable non-small cell lung cancer involves concurrent platin-based chemotherapy and radiotherapy.

Urinary bladder cancer

Concurrent chemoradiotherapy was shown to ensure better survival as compared to radiotherapy alone in the case of invasive urinary bladder cancer [73]. However, compared to radical cystectomy, chemoradiotherapy is associated with lower median of overall survival (32.8 *vs.* 36.1 months) [74, 75].

Head and neck cancers

The first study which showed significant advantage of the combined treatment with 5-fluorouracil and cisplatin as compared to radiotherapy alone was done for nasopharyngeal cancers (five-year overall survival of 67% and 37% respectively) [76]. There were over 100 randomised studies concerning chemoradiotherapy of head and neck cancers, showing absolute increase of five-year overall survival by 6.5%, prolonged time to progression, improved local control and increased chance of organ preservation [77]. Better results were achieved with concurrent than sequential chemoradiotherapy – both as the radical therapy and as post-operative treatment [78–80]. Currently a standard method of treating patients with locally advanced head and neck cancers is concurrent cisplatin-based chemoradiotherapy. However, this management is associated with intensified early and late adverse effects.

Conclusions

It has been demonstrated that chemoradiotherapy brings significant benefits in local control of the disease, organ preservation and overall survival of patients with some cancers.

However, concurrent chemoradiotherapy is more toxic than chemotherapy alone and radiotherapy alone or sequential application of these methods. This concerns both early and late complications and it may have negative impact on the patients' quality of life. Further studies are needed to optimise combined treatment. Nowadays, addition of targeted treatment and immunotherapy to chemoradiotherapy is already changing standardsof cancer treatments There are many trials underway to assess effectiveness and potential toxicity of particular scheme combinations.

The basic prerequisite for good combined treatment of cancer is proper diagnosis and its comprehensive organization, giving the opportunity to make the right clinical decisions by multidisciplinary teams.

Conflict of interest: none declared

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Received: 11 Aug 2022
Accepted: 24 Aug 2022

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