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Refresher course: Combined treatments in cancer radiation therapy

Chemoradiation: Why, what, for whom?

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The addition of chemotherapeutic agents to radiation has contributed to improve clinical outcomes in most patients with solid tumours and is representing, nowadays, the standard of treatment.

1. Why? Rational for the concurrent use of radiotherapy and chemotherapy

Spatial cooperation mechanism describes how radiation treats the primary location while chemotherapy is added to deal with systemic spread. In this approach, the effectiveness of the chemotherapeutic agent is critical in the success of the combined treatment and is well know that in common solid tumours chemotherapy can seldom achieve a survival fraction lower than 10^{-6}. As spatial cooperation is, indeed, targeting different anatomical sites and full doses of chemotherapy and radiotherapy are required, the optimal combination of both modalities of treatment is sequential.[1]

Citotoxic enhancement explained how the capacity of chemotherapy to modify the cell response to radiotherapy can provide a greater effect on cell survival than it would be expected from the mere additivity of their independent effects. That benefit relies commonly on increasing in the initial DNA damage caused by radiation, interfering in the cell capability of repairing DNA damage, temporally modulating the cell cycle. Despite that fact, toxicity caused by radiation is expressed locally while drugs cause mainly systemic toxicity, even when local toxicity can be increased by their simultaneous use. Concurrent use of chemotherapy and radiotherapy is mandatory if this citotoxic enhancement is aimed to be obtained.[1]

2. What? Main chemotherapeutic agents use concurrently with radiotherapy

2.1. *Platinum compounds*

Cisplatin and its analogues, increase the effect of radiation through the formation of toxic platinum intermediates in the presence of free radicals, the fixation by cisplatin of otherwise reparable DNA damage primarily caused by radiation, the increase of cisplatin cellular uptake after radiation, a synergistic disruption in cell cycle and the inhibition of DNA damage repair.[2]

2.2. *Fluoropyrimidines*

5-Fluoruracil (5-FU) and its prodrugs have shown S-phase specific toxicity, a phase in the cycle when the cell is particularly resistant to radiation induced damage.[3] Protracted infusion is required to achieve optimal radiosensitization, thereby a stable concentration of an orally given prodrug as capecitabine can provide the same results and, indeed, is replacing protracted infusion of 5-FU in some indications.

2.3. *Gemcitabine*

Gemcitabine produces an increase in radiosensitivity even at nontoxic concentrations. The interference with DNA synthesis and repair mechanism caused by the depletion of phosphorylated deoxynucleotides through the inhibition of ribonucleotide reductase has been claimed to be the

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underlying mechanism of enhancement.[4] Moreover, that depletion is leading to cell accumulation in S-phase, so cell cycle redistribution must be simultaneous with deoxyadenosine triphosphate pool depletion.

3. For whom? Main clinical indications of concurrent chemoradiation

The role of chemoradiation in the treatment of locoregional disease is preponderant, gaining new indications onward the basis of solid scientific evidence.

Head and neck squamous cell carcinoma is, probably, the best-studied indication. Meta-analysis have shown a significant benefit in survival (OS 5 years benefit: 8%) when chemotherapy is given concurrently with radiation, being the benefit higher in patients receiving platinum-based chemotherapy.[5,6]

A risk of death reduction of 14% has been shown in non small-cell lung carcinoma for the concurrent treatment when compared with radiotherapy alone, but oesophagitis, anaemia and neutropenia are also significantly increased.[7]

In limited stage small cell carcinoma, concurrent chemoradiation improved overall survival but the optimal combination and timing is conflicting.[8]

An absolute overall survival improvement by 10% has been shown by the addition of chemotherapy, mainly cisplatin, to radiation in cancer of the uterine cervix, with a parallel increase in haematological and gastrointestinal toxicity.[9] The benefit of induction chemotherapy has also been explored. Despite a trend to survival benefit in those schemes containing cisplatin doses over 25 mg/m^2, all other settings showed a detrimental effect on survival.[10]

Strong evidence supports the use of concurrent chemoradiation in gastrointestinal malignacies such as oesophageal cancer, gastric cancer, rectal adenocarcinoma and anal canal squamous carcinoma, as a preoperative, adjuvant or salvage treatment, depending on the disease.

4. Conclusions

Chemotherapy when applied concurrently with radiation has singular biological mechanisms and specific toxicity profile, that fact makes the difference between this concurrent setting and its use as a single agent. Radiation oncologists have to be proficient in its use and the specific knowledge necessary to manage concurrent chemoradiation schemes must be a comprehensive part of their training as it is recorded in the European Core Curriculum for Radiation Oncologists' training.[11]

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