Concurrent radiochemotherapy in the treatment of cancer. The best you can offer to the majority of your patients. Now!

Branislav Jeremić

Cancer is a deadly disease. It is so by virtue of its inherent biological characteristics, but also very much due to its insidious beginning and further development. This frequently leads to a large bulk of tumour cells presenting at the time of diagnosis and the majority of oncology patients seen worldwide have locally advanced or metastatic cancer. For such patients, radiation therapy (RT) and/or chemotherapy (CHT) are frequently used, either alone or, with increasing frequency in recent decades, as a combined treatment modality with curative intent.

There are now several decades of experience with combined RT and CHT. Many tumour sites, histologies and stages of disease have been the subject of intensive pre-clinical and clinical investigations. We have also witnessed tremendous change in technological aspects (of RT), with the passage from 2D to 3D RT to 4D to IMRT and IGRT and further to stereotactic RT, protons and carbon ions, all leading to more precision in treatment delivery. We have gathered enormous experience with new drugs, from second generation (e.g., cisplatin, etoposide) to third generation (e.g., paclitaxel, vinorelbine) to targeted agents (e.g., cetuximab). We have also not only investigated efficacy of various RT/drug combinations, but also gathered precious information about the side effects of such, usually intensified, treatments.

Well, then, what we have learned, so far, and what is the current status of combined RT and CHT? Due to the limited space envisaged for this Editorial, only some of the major findings will be summarised and some specific and very important aspects highlighted. Readers are encouraged to further explore particularities of combined RT and CHT in various tumour types in the literature.

We have learned that among several possible combinations, especially regarding timing (sequencing) of administration of RT and CHT, the two most common ones are

sequential (frequently called neoadjuvant/induction CHT followed by RT) and concurrent RT/CHT. These two types of administration are not only easy to directly compare in many tumour sites, but they can also be easily understood from the standpoint of four possible exploitable mechanisms of combined RT and CHT, as postulated more than 30 years ago by Steel and Peckham [1].

Data from multiple prospective randomised trials and meta-analyses clearly identify concurrent RT-CHT as the standard treatment option in many tumour types and sites such as head and neck, lung or cervix, given either as exclusive or in postoperative setting (e.g., head and neck cancer). Similarly to these, the majority of gastrointestinal cancers, some genitourinary cancers as well as some brain tumours are also treated this way. Exceptions exist, most notably breast cancer, prostate (though with hormones) and some bone and soft tissue sarcomas, where concurrent RT/CHT studies are lacking but some are already underway. Superiority of concurrent RT/CHT over RT alone was achieved due to improved loco-regional tumour control, which is in sharp contrast to induction CHT studies, which always improved overall survival (over RT given alone) due to improved distant metastasis control. Excellent examples for the two observations are head and neck cancer, lung cancer and cervix cancer. When considered from the standpoint of exploitable mechanisms, concurrent RT/CHT offered improvement due to CHT-induced enhancement of RT effects, showing that there is an interaction between the two treatment modalities due to concurrent administration. In induction CHT studies, there was no interaction (separate administration) and therefore no enhancement of RT effects by CHT. When directly compared, such as in the most recent meta-analysis in locally advanced non-small-cell lung cancer [2], concurrent RT/CHT was shown to be superior to induction CHT.

For us radiation oncologists, there is only one way of combining RT and CHT: *concurrent RT/CHT*. We target loco-regional disease, not the distant one (or microscopic one *per se*). Therefore, we are interested in improving results with the use of RT and drugs/compounds that should preferentially act on the same loco-regional level (i.e., within the RT treatment field), regardless of whether CHT also exhibits effects systematically. Naturally, many questions

B. Jeremić (✉)
Institute of Lung Diseases
21204 Sremska Kamenica
Serbia
e-mail: nebareje@gmail.com

remain, and there are great opportunities for translational and pure clinical research. Dose, fractionation and volumes are just a few of the RT-related issues, while type, choice, combination and administration are just a few of the CHT-related issues that need further optimisation.

Concurrent RT/CHT has frequently been demonised as being too toxic. In some cases this was the true since the community of radiation oncologists became victims of both convenience in administration and the CHT concept of MTD, meaning the bigger/higher the better. We chose the convenient administration of high doses of CHT concurrently to RT once every, for example, 3 weeks (once weekly, at best!), which produced more toxicity and only occasional (temporary) RT enhancement. The latter has clearly been shown to be inferior to more protracted/fractionated RT (e.g., bid fractionation) and CHT (e.g., low-dose daily CHT or CI CHT) administration in many laboratory and clinical studies. More labour led to more complaints about busy RT departments with few accelerators, physicians and (very much!) nurses and long waiting lists. This last issue was the icing on the cake against a policy of concurrent RT/CHT. Medical oncologists frequently asked radiation oncologists to start treatment while the patient was waiting for treatment planning CT, usually promised to take place in 2–3 weeks (conveniently enough time for 2 cycles of induction CHT!). There is a very clear reminder for those who had succumbed to these “Good Samaritans” in the study of El-Sharouni et al. [3], which compared CT scans pre-and post-induction CHT in lung cancer. During the waiting period (for planning the CT scan and start of RT), a total of 41% of all tumours became incurable. This important finding clearly shows the accelerated repopulation of tumour clonogens Better put, even if you may have thought that response to induction CHT occurs (and that it matters), actually the opposite happens: surviving tumour clonogens repopulate during and post-CHT (all before the main treatment modality, i.e., RT, starts), they do it fast and tumours regrow to the state of incurability by the time RT is instituted.

Additionally, concurrent RT/CHT is not only clinically and radiobiologically superior to induction CHT, but it also gives enormous opportunity for preclinical investigation, as was identified as one of the major pathways by NCI about ten years ago [4]. It can provide an opportunity to embark on various mechanistic-based studies to identify major characteristic of synergism i.e., enhancement of the RT effects by a drug/compound. To extend this and since translational research should ideally be seen as a two-way road

(lab to clinic, back and forth), enhancement of RT effects by a compound would provide a necessary framework and a platform for continuous investigations and optimisation of concurrent RT/CHT.

Finally, it must be remembered that terminology is a tricky thing. Who does not pay attention can be easily fooled. Especially in the US, the terminology used in recent decades to describe combined radiotherapy (RT) and chemotherapy (CHT) was “chemoradiation”. It became a necessary ingredient for any study protocol, published paper or presentation title, always unconsciously and adversely influencing the audience. As the title of this editorial clearly points out, it is wrong. The only term that appropriately describes concurrent RT and CHT is *radiochemotherapy*. If one gives 65–70 Gy of RT and concurrent either daily or weekly CHT or even more protracted CHT (i.e., cisplatin, 100 mg/sqm q 3 weeks), how this can be called “chemoradiation”? “Chemoradiation” may have been a more appropriate term in earlier times, when one started with CHT (induction, neoadjuvant type of administration). Since this (induction) sequencing is inferior to the concurrent one, the term “chemoradiation” should definitely belong to the museum of history of our failures. Do not forget that RT is the mainstay of the treatment and CHT is used to support these effects. Therefore, radiochemotherapy should be preferentially used as the term [5] appropriate for all concurrent regimens, deemed today as the standard of treatment in many tumour types and stages, as clear evidence suggests [6].

While this editorial targets the broad readership of the journal, it is particularly aimed at young oncologists, both residents and staff physicians. It is expected of them “to drink from this healthy well”, grow strong in the knowledge and skill of practising *radiochemotherapy* when indicated and persist to various non-medical and medical reasons that overshadow their clinical practice. The recent SEOR-EEOR course in Madrid (organised by Drs Hervas and De la Torre) [7] is an excellent example of how joint forces (specialists, professional society) in Spain can act to foster and boost efforts in using concurrent *radiochemotherapy* as the standard treatment option in the majority of patients with cancer we see and treat nowadays. A well structured agenda included an excellent manual (edited by Dr Ramos) [8] of the most common radiochemotherapy schedules, toxicity scoring and guidelines on how to medically treat them. There is no better tool for radiation oncologists, with a manual format perfectly matching doctors’ white coat pockets.

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