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LETTERS TO THE EDITOR

Reirradiation: hopes and concerns of the radiation oncologist

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To the editor: The 19th National Congress of the *Associazione Italiana di Radioterapia Oncologica*, held in Bologna from 14 to 17 November 2009, addressed 20 topics regarding radiotherapy in practice[1]. As in previous years, the experience of many Italian radiotherapy centers was reported. Because of the poor data and limited number of articles in the literature, one topic was the object of particular interest for radiation oncologists: repeated radiation treatment and the tolerance of healthy tissues in relation to the availability of new technologies. Twelve Italian experiences related to reirradiation were reported at the National Congress as oral presentations or posters[1].

Improvements in the efficacy of anticancer therapies and increased tumor detection at early stages in the last decades have led to a new phenomenon: patients in need of re-irradiation are found with increasing frequency.

Radiation retreatment is a problematic issue to resolve in clinical practice: it requires knowledge of the possibility of unforeseen toxicity risks in healthy tissue[2]. The radiation oncologist must consider many parameters before prescribing retreatment with radiation. Key questions to be addressed are: What is the endpoint of retreatment? What is the reirradiation intent? Reirradiation may be useful as a palliative approach for local-regional relapse or may be indicated to obtain or maximize local control of tumor recurrence, especially in the absence of other disease sites. Another case is represented by a second primary tumor in the area of previous radiation treatment: in this event the patient could need local radiation therapy with radical doses. This situation is more complex because of the requirement of a high prescription dose, frequently limited by the previously received dose to the same area.

The feasibility of reirradiation depends on previous doses and fields, the time between irradiation and reirradiation, the general conditions of the patient related to life expectancy, and alternative treatment options.

With regard to dose tolerance in reirradiation, there is no consensus about the dose limits to normal tissues involved in the field of previous radiotherapy. The maintenance of functional activity in the preirradiated field should be an absolute priority[2]. If there is a loss of function caused by previous radiation damage, radiation retreatment is not recommended. Few data on the time interval issue are available in the literature and most are from preclinical analyses: the minimum interval between 2 radiation treatments has not been clearly established. It might be considered a sound approach to allow for an interval longer than the period in which the most common late side effects would be expected[1]. This depends, however, on previous doses to organs at risk and the type of tissue damage repair. Complete restoration of early radiation damage in some tissues, such as skin or oral mucosa, ranges from 12 days to 90 days[3,4].

Stem cell reserve could require more time despite the fact that the parenchyma appears macroscopically and morphologically restored[2,5]. For late damage, tissue recovery is variable and 5 to 6 months may be necessary for many tissue types, as reported in preclinical studies[6-8]. As shown by preclinical data, there is no consensus about cumulative maximum tolerance doses and minimum time to recovery between 2 courses of radiotherapy for each type of healthy tissue. The few clinical data available in the literature are extremely heterogeneous[1,9-14]: various techniques (3-dimensional conformal radiotherapy, intraoperative radiotherapy, brachytherapy, intensity-modulated radiotherapy [IMRT], stereotactic radiotherapy) were reported in the same review; curative-intent and palliative-intent retreatments were included in the same groups of data analysis; radiation side effects were recorded with various toxicity scales in different centers. The prescribed retreatment doses are consequently decided upon on a purely empirical basis. A cumulative toxicity risk evaluation with the overlap of field/isodose curves of the 2 treatments or with the analysis of modern biological parameters (NTCP)[2], if available, could be a way to minimize uncertainty regarding toxicity.

The ideal modalities of reirradiation involve other critical points, including a better definition of the target to be reirradiated. In most cancer patients, PET/CT could be highly useful before reirradiation for better definition of disease recurrence and disease restaging[15]. Setup accuracy is another crucial point: immobilization devices are essential to reduce setup errors[16]. PET/CT in a single session compared to PET and CT in 2 different phases can minimize setup errors and optimize image coregis-

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tration[17]. "Dose sculpting" on active tumor with IMRT is a helpful approach to minimize the radiation dose to previously irradiated tissues[18]. Image-guided radiation therapy (IGRT) reduces repositioning errors and is used to monitor the treatment region[19]. Helical tomotherapy is an example of an advanced radiotherapy modality that combines IMRT with a helical delivery pattern and integrated IGRT system. The capacity of this technique to reduce uncertainties in patient setup and to produce extremely steep dose gradients allows ideal radiation delivery with dose painting to the target while sparing surrounding normal tissues[20]. The largest experience in terms of the feasibility and safety of radiation retreatments was reported with IGRT/IMRT using tomotherapy in 40 patients[1]. Other new developments such as volumetric arc therapy and CyberKnife or stereotactic radiosurgery offer new treatment possibilities in radiation retreatment: recent interesting Italian experiences in these fields were presented at the National Congress[1]. Considering the continuous advances in more detailed cancer imaging and safer radiation technology, new clinical data are awaited to confirm the promising results of these and other initial experiences, suggesting new possibilities to reirradiate cancer patients in selected cases.

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Is it possible to optimize the use of targeted therapies in the treatment of renal cell carcinoma?

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To the Editor: Renal cell carcinoma (RCC) is a neoplasm for which important advances in terms of biological, molecular and therapeutic knowledge have been achieved. The discovery of some pathogenetic mechanisms strictly depending on gene mutations led to the identification of angiogenesis as the key factor in tumor cell proliferation. On the basis of a sound preclinical rationale, given by the inhibitory effect of some agents on proangiogenic growth factors such as VEGF and PDGF and specific pathways related to tumor growth such as m-TOR, clinical investigations with targeted agents able to selectively interfere with the mechanisms underlying angiogenesis have been undertaken.

In the last few years, the therapeutic scenario has changed from cytokines alone, usually effective in selected patient populations, to multikinase inhibitors (sorafenib[1], sunitinib[2]), monoclonal antibodies (bevacizumab[3]), and m-TOR inhibitors (temsirolimus[4], everolimus[5]). This scenario is expected to broaden even more following the recent approval of pazopanib[6] by the FDA and the availability of data from advanced-disease clinical trials evaluating the efficacy of axitinib, regorafenib, cediranib and volociximab.

The results of the pivotal trials performed to obtain the approval of these agents have defined a treatment algorithm for the management of metastatic RCC based on different clinical, biological and histological factors. However, the considerable heterogeneity of RCC and its complex natural history, along with the safety profile of the different agents, often make the application of a particular therapeutic approach rather difficult. Moreover, the availability of several drugs in the same disease setting frequently requires a tailored therapeutic program. As a matter of fact, while clinical data support the use of sunitinib as the standard treatment for low- and intermediate-risk advanced RCC, the efficacy of the bevacizumab + interferon-alpha combination in the same patient population has opened a debate on identifying patients' responsiveness to different treatments.

It must be emphasized that in selected cases of this population sorafenib and high-dose interleukin-2 is also an option. Consequently, besides the preference for oral or intravenous administration, comorbidities and patient age could lead the clinician towards the most appropriate therapeutic decision. Besides such considerations, another key point to consider is the possibility to achieve the best disease control with the appropriate sequential use of the available targeted agents in patients with disease progression.

So far, data from 2 randomized clinical trials in pretreated patients with advanced RCC are available: one with sorafenib and one with everolimus. Both studies showed a lack of cross-resistance and justify sorafenib or everolimus treatment in patients progressing on previous treatment with either cytokines or sunitinib and/or sorafenib regimens. Other retrospective studies pointed out the lack of cross-resistance between sunitinib and sorafenib, thus supporting the use of either of these drug in patients progressing on the other[7,8]. In addition, both these tyrosine kinase inhibitors have shown efficacy upon failure of a bevacizumab-based regimen. Briefly, several clinical data support the sequential use of targeted agents in the clinical management of advanced RCC.

An as yet unsolved issue is the definition of the best therapeutic sequence; in other words, whether the previous use of a given agent could possibly foster better disease control. Obviously, only a prospective randomized trial will be able to address this issue. However, notwithstanding the lack of evidence, some comments can be made:

- the often unpredictable course of the disease and changes in the clinical features over time can prevent clinicians from identifying the optimal therapeutic sequence;
- the different mechanisms of action of targeted agents and the clinical evidence available so far do not allow to define which therapeutic sequence can be considered as the best available;
- RECIST criteria not always allow to fully evaluate the treatment response to targeted agents. For a correct assessment of the disease it is therefore recommended to take into consideration also clinical and laboratory findings;
- maintaining the targeted agents' dose intensity is essential to ensure the best results in terms of therapeutic efficacy; therefore, careful and appropriate management of side effects during treatment is warranted;

Key words: renal carcinoma, targeted therapies, angiogenesis, multikinase inhibitors, vascular endothelial growth factor.

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– combination regimens consisting of 2 targeted agents or a targeted agent plus cytokines are affected by an increase in the number and severity of side effects, often making treatment continuation at full dosage of both agents difficult[9,10];
– it is mandatory to personalize the therapeutic program according to prognostic factors such as MSKCC, tumor histology, disease site, and presence or absence of the primary tumor.

Therefore, in the absence of clear evidence supporting a specific therapeutic approach, the oncologist should consider first the treatment expected to obtain the best results in terms of efficacy, according to the clinical status of the patient. Further studies will hopefully be able to supply more exhaustive information about the correct use of targeted agents in order to improve the outcomes of patients suffering from RCC.

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