Re: Late Effects From Radiation Therapy: The Hits Just Keep on Coming

All things are poison and nothing is without poison, only the dose permits something not to be poisonous. Paracelsus (1493–1541)

In his recent editorial (1) regarding our article on the increased risk of stroke and transient ischemic attack following Hodgkin lymphoma (2), Longo criticized the use of radiotherapy in the treatment of Hodgkin lymphoma and stated that chemotherapy is as effective as combined modality treatment and proven to be safe. We argue below that Longo overestimated the efficacy of chemotherapy alone in the treatment of Hodgkin lymphoma while at the same time underestimating the toxicity of this treatment. The possible value of radiation for patients with Hodgkin lymphoma was not recognized, whereas its toxicity was overrated. Moreover, Longo’s criticism against the use of radiotherapy was based on outdated concepts regarding radiation toxicity.

Longo’s suggestion that Hodgkin lymphoma patients can be cured with chemotherapy alone is not supported by present evidence. Cure rates following chemotherapy alone are not nearly as good as those for combined modality treatment (3). Certainly, chemotherapy may well be sufficient for a portion of patients with Hodgkin lymphoma, but not for all. The rationale for radiotherapy is based on the observation that relapses usually involve initially involved sites and the finding that radiotherapy reduces recurrence rates. Of note are the initial results of a meta-analysis that showed improved overall survival for early-stage Hodgkin lymphoma patients treated with combined modality therapy compared with patients treated with chemotherapy alone (4).

Longo stated that treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is safe and that reports on fatal toxicity are only anecdotal. In our opinion, a 2%–3% fatal toxicity (5) and an eightfold increased risk of cardiac mortality (6) as reported following ABVD are not negligible. Longo stated that there is no evidence for lower toxicity of reduced radiation doses and volumes. We disagree. Clear reductions of breast cancer risk have been shown following radiation at lower doses and to more limited tissue volumes (7,8). Furthermore, the risk of radiation-associated cancer does not have a bell-shaped but a linear relationship to radiation dose, as has been shown for breast and lung cancer following Hodgkin lymphoma (9,10). In addition, there is growing evidence indicating dose–effect and dose–volume relationships for radiation-associated cardiovascular disease (11).

It is essential to realize that our article involved patients treated in the past with radiation volumes, doses, and techniques that are no longer used. However, the results of our investigation are important to devise risk-reducing strategies for survivors at high risk of late radiation-induced effects and to adapt treatment strategies for future patients that reduce the risks of late effects as much as possible.

In conclusion, changes in therapy should be made only in the context of carefully designed clinical trials that evaluate whether the overall efficacy of treatment is maintained. Treatment of patients with Hodgkin lymphoma should consist of chemotherapy followed by radiation if indicated by patient and tumor characteristics and the patient’s response to chemotherapy as evaluated using modern techniques, such as fluorine-18-fluorodeoxyglucose positron emission tomography scans. When radiotherapy is applied, volume and dose should be as limited as possible and modern imaging and radiation techniques should be used.

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