VOLUME 25 · NUMBER 19 · JULY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

How Can We Determine the Role of Radiotherapy in the Treatment of Localized Aggressive Non-Hodgkin's Lymphoma?

TO THE EDITOR: In the recently published phase III trial by Groupe d'Etude des Lymphomes de l'Adulte (GELA)—a group of authors who are opponents of adjuvant radiotherapy in treatment of aggressive localized non-Hodgkin's lymphoma—the role of radiotherapy was questioned again.[1,2] However, we believe that there are certain drawbacks in their trial. First, primary failures are two times more common in the group assigned to adjuvant radiotherapy (6% *v* 3%), although the two groups were treated with the same chemotherapy regimen (four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]). Secondly, more than 10% of the patients allocated to adjuvant radiotherapy did not receive it, and in one fourth of patients, this was attributed to poor response obtained with CHOP chemotherapy. Thus, the two groups, although they appear to be well-balanced with respect to stage, age-adjusted international prognostic index scores, and other factors such as bulky disease, do not seem similar with respect to treatment sensitivity. Another drawback of the study that may have affected the results was the administration of radiotherapy to the majority of the partial responders in the CHOP alone arm (six of eight patients). Despite all of these factors negatively influencing the results of CHOP plus radiotherapy, the total number of relapsed patients in this group was lower than the total number of relapsed patients treated only with chemotherapy (66 *v* 79 patients). More interestingly, although not mentioned in the study, radiotherapy achieved its objective, as the infield failure rates decreased more than half by radiotherapy when compared with the group receiving only chemotherapy (21% *v* 47%).

Fewer lymphoma relapses (66 *v* 79 patients) despite higher lymphoma-related deaths (70 *v* 65 patients) in the CHOP plus radiotherapy arm seems paradoxical, and the authors claim that the administration of radiotherapy alters the pattern of localization of relapses, but does not decrease the overall rate. In their reply[3] to correspondences concerning the GELA's former trial, they state that the aim of first-line treatment of localized lymphoma is to improve survival rather than to control local disease. But how can we talk about cure without controlling malignancy locally? In contrast to many other malignant diseases, negative effect of local recurrence on survival in lymphomas may be offset by the efficacy of salvage treatments. But still the adverse effect of bulky disease on survival has been demonstrated in a multivariate analysis.[2]

Another important point that must be mentioned, which was also observed in this study, was the different sensitivity and outcome of aggressive non-Hodgkin's lymphomas to the same treatment. This difference may depend on many and even unknown factors such as WHO classification, site of origin of lymphoma, and pattern of gene and protein expression, which may be different even in the same lymphoma type.[4]

In order to prove the benefit of radiotherapy in localized aggressive non-Hodgkin's lymphomas, it would be better to stage patients with positron emission tomography scanning rather than with conventional imaging, and to include patients only with a single WHO-classified disease entity with same localization, size, and International prognostic index scores. In this way the groups can be made more homogenous with respect to treatment sensitivity.

Cengiz Gemici and Taflan Salepci

Dr Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, Turkey

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Bonnet C, Fillet G, Mounier N, et al: CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 25:3958-3964, 2007

2. Reyes F, Lepage E, Ganem G, et al: ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 352:1197-1205, 2005

3. Hoecht S, Hinkelbein W: Treatment of localized lymphoma. N Engl J Med 352:2449-2451, 2005

4. Armitage JO: Defining the stages of aggressive non-Hodgkin's lymphoma - a work in progress. N Engl J Med 352:1250-1252, 2005

DOI: 10.1200/JCO.2007.11.1450

IN REPLY: We thank Drs Gemici and Salepci for their interest in our study.[1] We are not opponents of adjuvant radiotherapy in aggressive localized non-Hodgkin's lymphoma. In our article, we analyzed the mature data of a trial initiated in 1993 to compare radiotherapy versus nothing after four cycles of chemotherapy.

According to the comments by Gemici and Salepci, primary failures were twice as common in the group assigned to radiotherapy. Indeed primary failures at the end of treatment were observed in 17 (6%) of 295 assessable patients assigned to the combined modality as compared with nine (3%) of 273 patients assigned to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) alone. However, these values are not statistically significant ($P = .16$).

As presented in Table 1, there is no significant difference in relapse rate between the two arms. The death rate related to the lymphoma is the same in both groups (24%). Gemici and Salepci are right when they state that more than 10% of the patients allocated to adjuvant radiotherapy did not receive it. As mentioned in Results section of our article, 12 of 299 patients allocated to chemotherapy could not be irradiated because of progression (according to the protocol) or death during CHOP induction and 23 could not receive

Downloaded from jco.ascopubs.org by Guy Jerusalem on August 13, 2007 from 139.165.96.129.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

Table 1. Results According to Different Analyses

Type of Analysis	CHOP Alone No.	CHOP Alone %	CHOP + Radiotherapy No.	CHOP + Radiotherapy %	P
Intention to treat	277		299		
Relapse	79	29	66	22	.07
Death due to lymphoma	65	24	70	24	.98
5-year EFS		61		64	.6
5-year OS		72		68	.5
As treated	255		259		
5-year DFS		64		71	.2
5-year OS		75		75	.6
Restricted to DLBCL	187		223		
5-year EFS		63		62	.7
5-year OS		74		67	.3
Restricted to patients with limited-stage disease	248		270		
5-year EFS		61		66	.3
5-year OS		70		72	.9

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; EFS, event-free survival; OS, overall survival; DLBCL, diffuse large B-cell lymphoma; DFS, disease-free survival.

radiation because of a medical decision by local investigators or refusal of the patients. Such protocol deviations are inescapable in a trial conducted on a multicenter basis and reflect real medical practice. In our opinion, they legitimize the analysis performed on an intention-to-treat basis. Because one might argue that such protocol deviations might have influenced negatively the results of CHOP plus radiotherapy, we performed an as-treated analysis for patients in complete remission at the end of treatment. The as-treated analysis (not included in our article) compares the outcomes of complete response patients who have or have not received radiotherapy. No significant difference is observed in terms of disease-free or overall survival rates (Table 1).

We agree with comments concerning the histologic and stage-adapted International prognostic index heterogeneities of the included cohorts. Analyses restricted to patients with DLBCL fail to demonstrate any advantage of radiotherapy (Table 1). Similarly, analyses restricted to patients with limited disease (excluding patients with stage II bulky disease) do not affect our conclusions.

Finally, we know that the addition of anti-CD20 to CHOP improves the results in term of complete response rate, event-free survival, and overall survival, particularly in a subset of elderly patients with a low-risk age-adjusted International prognostic index score.[2,3] In our study, we observed a 5-year overall survival of 72% after 4 cycles of CHOP repeated at 21-day intervals (CHOP 21). By adding rituximab, we hoped for an increase of approximately 15% in survival.[3] Thus, taking into account the percentage of deaths related to natural causes in this elderly population, the demonstration of a potential benefit of radiotherapy will be even more difficult to assess in a study including rituximab.

Georges Fillet and Christophe Bonnet

Department of Hematology, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Bonnet C, Fillet G, Mounier N, et al: CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 25:3958-3964, 2007

2. Coiffier B, Lepage E, Brière J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:280-282, 2002

3. Feugier P, Van Hoof A, Sebban C, et al: Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma : a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 23:4117-4126, 2005

DOI: 10.1200/JCO.2007.11.6004

Sunitinib Malate and Multiple Receptor Tyrosine Kinases Inhibitors: Are They Also Novel Drugs for Chronic and Neurophatic Pain?

To the Editor: Recently, I read with interest the article "Sunitinib: From Rational Design to Clinical Efficacy"[1] published in the March 1, 2007, issue of the *Journal of Clinical Oncology*. Interestingly, Chow et al reported a range of in vitro and in vivo RTK (RTKs are transmembrane proteins at the cell surface that transduce extracellular signals to the cytoplasm, which may be inhibited by sunitinib) targets that have been further validated by the clinical activity observed in patients treated with sunitinib and other agents inhibiting these pathways. "However," they added, "the contribution and/or dominance of inhibition of which specific RTK pathways are associated with sunitinib-induced responses are not well understood and are under active investigation."[1]

The authors reported data on preclinic and clinic phase I, II, and III trials. They correctly concluded that although initially promising, RTK targets need additional validation in phase II/III trials. Overall, they said, the clinical benchmarking of an agent that influences multiple signaling pathways of tumor, stromal, and endothelial compartments should stimulate additional research into the biology of responsive tumors. Challenges ahead include the ability to combine sunitinib with other therapies where toxicities may be overlapping, optimization of dosing regimens, and additional assessment and development of patient selection criteria. Reading this interesting article, I recalled another recently published article[2] where the authors discussed how the past decade has been characterized by a better understanding of physiology of chronic pain. These other authors reported that nerve-growth factor (NGF),[2] "the founding member of the neurotrophin family of structurally related secreted proteins, binds to two types of receptors: a common receptor, p75NTR, which binds all neurotrophins with a similar affinity, and members of the trk family of receptor tyrosine kinases (trkA, trkB, and trkC), which bind

Downloaded from jco.ascopubs.org by Guy Jerusalem on August 13, 2007 from 139.165.96.129.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.