clinical questions without waiting years for results of a clinical trial to mature. The potential savings, in terms of time and money as well as patient costs, are substantial.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES

1. Federico M, Luminari S, Dondi A, et al: R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: Results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol 31:1506-1513, 2013

2. Olin RL, Kanetsky PA, Ten Have TR, et al: Determinants of the optimal first-line therapy for follicular lymphoma: A decision analysis. Am J Hematol 85:255-260, 2010

3. Rummel MJ, Niederle N, Maschmeyer G, et al: Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 381:1203-12010, 2013

4. Salles G, Seymour JF, Offner F, et al: Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. Lancet 377:42-51, 2011

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Reply to R.L. Olin et al

We thank Olin and Andreadis[1] for their interest in our article[2] that reported the results of a prospective, randomized, open-label multicenter phase III trial that was designed by the Fondazione Italiana Linfomi (formerly Intergruppo Italiano Linfomi) with the aim of identifying the most appropriate chemotherapy regimen associated with rituximab for the treatment of advanced follicular lymphoma (FL) requiring active therapy.

As clearly stated by Press and Palanca-Wessels in the editorial that was published with our study, "Few topics in the field of hematology/oncology have generated as much controversy and debate in the last 40 years as the proper management of patients with follicular non-Hodgkin lymphoma."[3(p1496)] When our study was designed in 2005, the three most common regimens used in the first-line setting of advanced, symptomatic FL were rituximab plus cyclophosphamide, vincristine, and prednisone; rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; and rituximab plus fludarabine and mitoxantrone. At that time, there were no comparative trials demonstrating the superiority (or noninferiority) of one of these treatment options compared with the others, and the results of the study conducted by Olin et al[4] had not yet been published. Therefore, a prospective, controlled, phase III clinical trial was the only available methodology to provide a definite answer to this question.

We congratulate Olin et al[4] for having reached precisely the same conclusions as those found in our study,[2] using a decision analysis approach. This approach is based on a meta-analysis of existing trials, which does not require any random assignment of patients and involves minimal financial resources. However, we would like to underline that a meta-analysis is possible only because of the results of robust, prospective, large, controlled clinical trials. In the absence of these contributions, a decision analysis cannot be performed. Moreover, we would like to point out some concerns regarding the absolute validity of the decision analysis, despite the conclusions being in line with those identified by our clinical trial. Some data were obtained from congress abstracts, which generally have reduced scientific relevance. Additionally, as declared by the authors,[4] only one study evaluating first-line rituximab plus cyclophosphamide, vincristine, and prednisone met the inclusion criteria for the decision analysis, creating concern about the imbalance in the quantity of available data for the three regimens. Furthermore, the estimates regarding first-line progression-free survival are likely to have been imperfect because of the lack of published information on the variances in progression-free survival data from clinical trials.

So far, randomized controlled trials continue to be the most rigorous way to determine whether a cause-and-effect relationship exists between treatment and outcome. Nonrandomized trials, or decision analyses, can suggest associations between an intervention and an outcome, but they cannot exclude the possibility that the association is caused by a linked third factor. Random allocation ensures that there are no systematic differences between the intervention and control groups for known and unknown factors that may affect the outcome.[5]

Finally, we do not recognize ourselves as Goliath. Our study was a fully academic, nonsponsored clinical trial that was conducted with very limited financial resources and was brought about only because of the strong commitment of many passionate clinicians, pathologists, molecular biologists, monitors, and data managers. Moreover, data collected in our study[2] allowed us to analyze the role of positron emission tomography in staging[6] and response assessment (manuscript in preparation), the role of minimal residual disease status in prognosis (manuscript in preparation), and the contribution of single nucleotide polymorphisms to prognostic stratification of FL that is treated with immunochemotherapy (manuscript in preparation).

In our opinion, decision analysis can be effective in the extrapolation of data provided by robust, prospective trials, which are still the basis for most advances in medicine, but cannot replace them.

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

REFERENCES

1. Olin RL, Andreadis C: David versus Goliath: Decision analysis predicts results of a large clinical trial in follicular lymphoma. J Clin Oncol 31:3608, 2013

2. Federico M, Luminari S, Dondi A, et al: R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: Results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol 31:1506-1513, 2013

3. Press OW, Palanca-Wessels MC: Selection of first-line therapy for advanced follicular lymphoma. J Clin Oncol 31:1496-1498, 2013

4. Olin RL, Kanetsky PA, Ten Have TR, et al: Determinants of the optimal first-line therapy for follicular lymphoma: A decision analysis. Am J Hematol 85:255-260, 2010

5. Sibbald B, Roland M: Understanding controlled trials: Why are randomised controlled trials important? BMJ 316:201, 1998
6. Luminari S, Biasoli I, Arcaini L, et al: The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: A retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. Ann Oncol 24:2108-2112, 2013

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Is Radiotherapy Needed for Pediatric Hodgkin Lymphoma?

To the Editor: Dörffel et al[1] recently reported results from the nonrandomized phase II German Society of Pediatric Oncology and Hematology–Hodgkin's Disease 95 (GPOH-HD95) trial involving the omission of radiotherapy for children and adolescents with Hodgkin lymphoma. They conclude that radiotherapy can be safely omitted in early-stage Hodgkin lymphoma in patients with a complete response. This statement does not seem justified.

Compared with their historical standard, Deutschen Arbeitsgemeinschaft für Leukämieforschung–Hodgkin's Disease 90 (DAL-HD90), radiotherapy significantly improved 10-year progression-free survival (PFS; 92% *v* 84%; $P = .004$) for all 165 patients. In the patient subset with early-stage disease (n = 66), radiotherapy did not improve PFS. Can the omission of radiotherapy be based on 66 patients compared with a historical control? More than 10 times as many patients are needed to show noninferiority. For example, Hodgkin's Disease 11 (HD11) was a noninferiority trial that involved 1,395 adult patients, and found that 20 Gy of radiotherapy was inferior to 30 Gy.[2]

Dörffel et al[1] claim that their results are consistent with those of previous randomized trials. The Children's Cancer Group (CCG) conducted a phase III trial evaluating whether radiotherapy could be omitted with a complete response after chemotherapy. The trial met early stopping rules because the event-free survival (EFS) was inferior in children who did not receive radiotherapy.[3] The EFS difference of 91.2% versus 82.9% ($P = .004$) in favor of radiotherapy persisted at 10 years, although the 10-year overall survival difference did not reach statistical significance.[4] Overall survival requires more power than EFS because the event rate is lower. Thus, because the CCG trial closed early as a result of inferior results without radiotherapy, it lacked power to show an overall survival benefit.

In my opinion, both trials indicate that radiotherapy is required in Hodgkin lymphoma, whereas the authors conclude the opposite. The combination of chemotherapy and radiotherapy should continue to be the standard of care for patients with pediatric Hodgkin lymphoma.

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REFERENCES

1. Dörffel W, Rühl U, Lüders H, et al: Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: Final results of the multinational trial GPOH-HD95. J Clin Oncol 31:1562-1568, 2013
2. Eich HT, Diehl V, Görgen H, et al: Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 28:4199-4206, 2010
3. Nachman JB, Sposto R, Herzog P, et al: Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 20:3765-3771, 2002
4. Wolden SL, Chen L, Kelly KM, et al: Long-term results of CCG 5942: A randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma—A report from the Children's Oncology Group. J Clin Oncol 30:3174-3180, 2012

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Reply to A.S. Reese

Approximately 90% of all patients with pediatric Hodgkin lymphoma (HL) achieve long-term remissions with standard first-line treatment, and approximately 95% of affected children and adolescents survive 10 years and more. The primary remaining therapeutic problem is thus minimizing the treatment burden and long-term toxicity while preserving high long-term progression-free survival (PFS) rates. As a consequence, it was a main goal in the tradition of trials by the Deutschen Arbeitsgemeinschaft für Leukämieforschung (DAL)/German Society of Pediatric Oncology and Hematology (GPOH) to subsequently reduce radiotherapy fields from extended to reduced involved fields and also to reduce radiotherapy doses to 20 Gy from 36-40 Gy.[1]

The GPOH–Hodgkin's Disease 95 (GPOH-HD95) trial investigated whether radiotherapy can be omitted in patients achieving complete remission (CR) with chemotherapy tailored to treatment group, that is, the initial tumor burden. The study provides evidence for what has been known for at least 50 years, namely, that radiotherapy is an effective treatment modality for HL. In intermediate and advanced stages, PFS of patients in CR without radiotherapy was inferior to that of patients not in CR who received radiotherapy.[2] Therefore, Reese[3] is correct in pointing out that our results do not warrant a general elimination of radiotherapy from the treatment of HL.

However, we claim that radiotherapy can be safely omitted in patients with early-stage HL who achieve a precisely defined CR after two cycles of vincristine, procarbazine, prednisone, and doxorubicin (OPPA) or vincristine, etoposide, prednisone, and doxorubicin (OEPA). Reese[3] is also correct in pointing out that we did not formally prove noninferiority in PFS in this particular group. This would have required randomization of radiotherapy versus none in this subgroup and an unfeasible sample size, even for an international study, given the prevalence of HL in this age group.

Our trial resulted in PFS of 97% at 10 years (SE, 2%) for 66 patients with early-stage disease who did not receive radiotherapy after achieving CR following chemotherapy. PFS was 92.2% (SE, 1.7%) for 262 patients with early-stage disease who received radiotherapy, given

