Predictors of early response and event-free survival in Hodgkin lymphoma (HL): PET versus CT imaging

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Introduction/Background

- Response directed therapy is an important concept in the management of Hodgkin Lymphoma (HL). In adult HL, risk stratification after early therapy response assessment with PET allows tailoring therapy for patients with adequate metabolic response. While PET imaging is standard imaging in adult HL, the clinical utility of FDG PET/CT in pediatric HL is not fully established.
- POG 8826 found that an early CR (after 3 cycles of chemotherapy) based on conventional imaging modalities predicted EFS (event free survival) while a late CR did not (Weiner, JCO 1997)
- POG 9425 used an early response based algorithm to titrate therapy based on rapid early response (3 cycles of ABVE-PC: adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide followed by 21 Gy radiation) or slow response (5 cycles of ABVE-PC before radiation) on gallium testing (Schwartz, Blood 2009)
- Early PET imaging has emerged as a predictor of EFS in HL, but comparisons of early response assessment by PET vs. CT are limited. Children's Oncology Group (COG) study AHOD0031 was designed to evaluate the paradigm of early-response-based treatment intensity using PET and CT scans, which were obtained after 2 cycles of ABVE-PC. The aim of this study was to directly compare PET vs. CT in terms of the ability to predict an early response to 2 cycles of ABVE-PC.

Methods

- Patients on study AHOD0031 were randomized to standard vs. early response-based therapy. Patients were eligible for enrollment if they were under age 21 with intermediate risk HL (excluding non-bulky IA/IIA, IIIB/IVB). Rapid early response (RER) by CT was defined as greater than a 60% 2-dimensional tumor reduction. RER by PET was defined as a negative (vs. equivocal/positive) scan after two cycles of chemotherapy.
- The ability of CT and PET to predict of EFS was also studied. Visual assessment was used to document PET response.
- Standard therapy included 4 cycles of AVBE-PC followed by radiation; the rapid early responders on the response based therapy arm were randomized to RT after two cycles of chemo vs. after 4 cycles
- Predictors of RER and EFS were derived from clinical and pathologic factors available in the COG database (for example, race, age, hemoglobin level, albumin level, ESR, and stage).

Results
1,136 patients were analyzed. Those with CT-based assessment of early response who had protocol-mandated, concurrent PET were included in an analysis of predictors of early response. Among the group, 770 patients were assigned to treatment with 4 ABVE-PC followed by 21Gy involved field radiation; this cohort was used to assess EFS.

On multivariate analysis, predictors of RER using CT imaging after 2 ABVE-PC included a large mediastinal mass (OR 0.41), nodular sclerosing histology (OR 0.45), age<13 (OR 1.48), and stage I disease (OR 2.31). Predictors of RER using PET imaging included large mediastinal mass (OR 0.78), ESR <20 (OR 1.37), and albumin <3.5 (OR 1.36).

On Cox regression analysis, both CT and PET were found to be independent predictors of EFS. While CT was predictive (HR 0.49, p=0.01), PET was of borderline significance (HR=0.69, p=0.10).

Clinical factors were also important predictors of EFS: the HR for Stage 4 disease was 2.41,(p=0.0014) , the HR for B symptoms was 2.05,( p=0.008), the HR for hemoglobin <10.5 was 1.62 (p=SS) and the HR was 0.48 for Black race (p=SS).

Author's Conclusions

Different predictors were identified for CT vs. PET RER and furthermore there were a greater number of predictive variables identified for CT response as compared to PET response. CT was more strongly predictive of RER than was PET after 2 cycles of chemotherapy.

Each modality may thus represent different aspects of the biology of response and therefore, each study should be considered in clinical decision making.

Clinical Implications

Predictors of CT and PET response are different. Use of both CT and PET as part of this study was informative. Functional response assessment by PET in conjunction with an anatomic response assessment by CT in pediatric HL patients might help to identify the group of patients for whom therapy can safely be de-escalated.

One issue that remains is the method of interpretation of the scans. In terms of interpretation of PET results, the PET response was not based on SUV, therefore a quantitative assessment was done for CT response whereas a qualitative assessment was used for PET response. Furthermore, there can be discrepancy among different reviewers in assessing a PET scan as positive. Because cutoff values for SUVmax reduction in determining good vs poor responders have not been established, personal review of PET imaging should be done with the nuclear medicine, the pediatric oncologist, and the radiation oncologist in cases for which a patient's response is not easily categorized.

Along these same lines, combined PET/CT scans to assess early response may prove to be preferable to performing these scans independently. Meanwhile standardizing response criteria for interim analysis is important.

Cure rates for pediatric HL are excellent, but late effects, particularly second malignant neoplasms, are a major concern. Thus, efforts have sought to de-escalate radiotherapy (including decreasing dose and decreasing volume) as well as chemotherapy in order to reduce toxicity without compromising survival rates. Current COG trials evaluate the elimination of radiation therapy in early responders, based on the hypothesis that early response to chemotherapy may identify tumors that are so chemosensitive that radiotherapy may be avoided. The ability to avoid over-treatment as well as under-treatment will hinge on improving sensitivity and specificity of imaging as well as clinicians appropriately interpreting the results of these studies.

Reference


