Malignant Lymphomas

The prognostic value of interim positron emission tomography scans combined with immunohistochemical data in diffuse large B-cell lymphoma

The treatment of hematologic malignancies is moving towards risk-stratified directed therapy, whereby treatment is based on the disease's biological characteristics and response to treatment. We investigated whether BCL2 and BCL6 status could add to the prognostic information yielded by an interim positron emission tomography (PET) scan in the ability to predict outcome. Negative interim scans and BCL2-negative status correlated with continuing remission (p<0.005) at a median follow up of 24 months.

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Less than 50% of patients with diffuse large B-cell lymphoma (DLBCL) remain disease-free for lengthy periods.[1,2] Better tools for predicting outcome are needed in order to be able to introduce risk-adapted treatment strategies. Although the results of interim fluorodeoxyglucose positron emission tomography (FDG-PET) after 2-3 chemotherapy cycles are a strong predictor of outcome, many FDG-PET-negative patients still experience relapse.[3,4]

Further prognostic information is increasingly being accrued from the disease biology that governs cell cycle kinetics and apoptosis. The relationship between the level of expression of the apoptosis-inhibiting BLC2 protein and the prognosis of DLBCL has been shown in several studies.[5-8] The aim of this study was to assess whether immunohistochemical staining for BCL2 and BCL6 could add to the prognostic value of interim FDG-PET. In this retrospective, hypothesis-generating study we analyzed 48 patients with DLBCL referred between 1996 and 2003 to the lymphoma clinic at Guys and St Thomas' Hospital, London, UK. Patients in this study were assigned a diagnosis of primary DLBCL according to the World Health Organization (WHO) classification. Lymphomas related to the acquired immune deficiency syndrome or organ transplantation were excluded. All patients had FDG-PET scans performed at the time of staging and later underwent interim FDG-PET scans during the course of chemotherapy: 33 patients after two cycles, eight patients after three cycles and seven patients after four cycles of chemotherapy. At study entry all patients had biopsy specimens stained to determine the presence of BCL2 and BCL6 protein expression. Staining was carried out using a doubling labeling procedure with Dako reagents (Dako Cymaticon, Glostrup, Denmark) on formalin-fixed, paraffin-processed tissues and was graded by two experienced hematopathologists. Progression-free survival and overall survival were analyzed using univariate survival analyses. The independence of other pre-treatment prognostic factors was tested with Cox regression analyses. The initial FDG-PET staging was abnormal in all 48 patients; these results are outlined in Figure 1 in a tree flow diagram. Twenty patients had positive interim PET scans while 28 patients became PET-negative at the interim scans. The tree flow diagram shows the rate of patients with progressive disease within the subgroups based on interim FDG-PET and BCL2/BCL6 status. The 20 interim FDG-PET-positive patients had a relatively high progression rate, which appeared unaffected by BCL2 status. In the interim FDG-PET-negative group, there was a large difference in progression-free survival, since six of 15 BCL2-positive patients relapsed within the follow-up period while all 13 BCL2-negative patients are in continued complete remission after a median follow-up of 24 months.

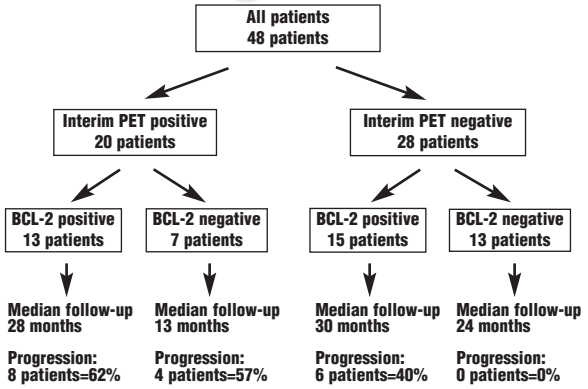

Figure 1. Outcome of treatment. Flow diagram showing the clinical outcome of patients in the four prognostic groups based on interim FDG-PET and BCL2.

Figures 2A and 2B show the highly significant difference in progression-free survival and overall survival between interim FDG-PET-positive and negative patients but Figure 2A also illustrates a considerable proportion of patients who eventually relapsed despite a negative interim FDG-PET. The influence of immunohistochemical status, with regards to the presence of BCL2 and BCL6, is shown in Figures 2C and 2D: BCL2 alone but not BCL6, was predictive of progression-free survival. The value of BCL2 and BCL6 for predicting progression-free survival was then examined within the PET-negative group, and is illustrated in Figures 2E and 2F. The first plot shows that all the patients with disease progression were in the BCL2-positive group, whereas no BCL2-negative patients experienced progression. The observed difference between the curves representing BCL2-negative and BCL2-positive patients was significant (log rank, p=0.016). The difference between the curves representing BCL6-positive and BCL6-negative patients, shown in the second plot, is not statistically significant (log rank, p=0.154). The same analysis was subsequently performed with patient age, presence of extranodal disease, and clinical stage. None of these parameters had significant predictive value for progression-free survival within the group of PET-negative patients.

The current study confirms the prognostic value of the results of an early interim FDG-PET scan regarding both progression-free and overall survival. Multivariate analysis showed that interim FDG-PET status and clinical stage were the strongest predictors of progression-free survival, independently of each other and the remaining factors. BCL2 was of significant predictive value for progression-free survival in univariate analysis, but lost its significance in multivariate analysis. At

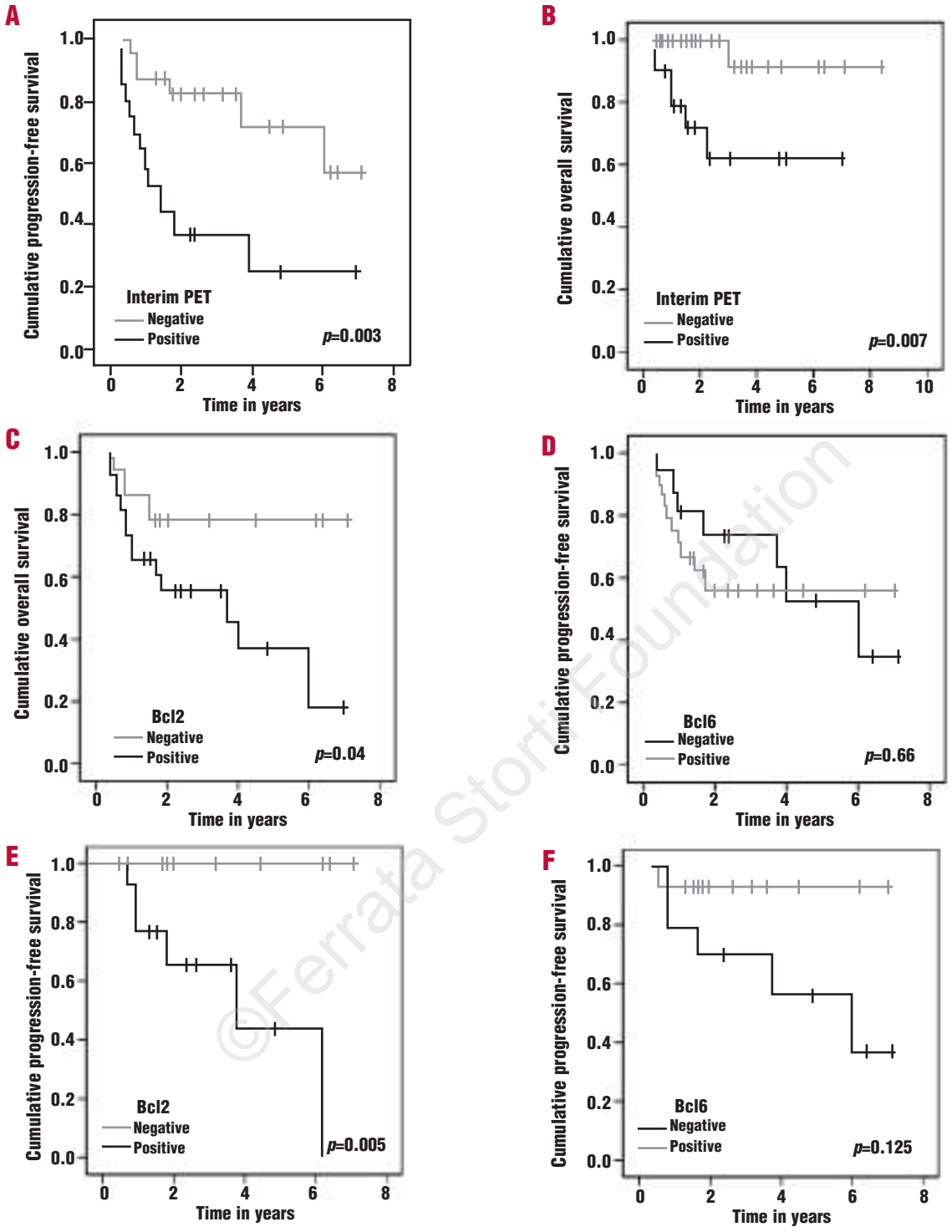

Figure 2. Survival according to FDG-PET, BCL2 and BCL6 status. (A) Kaplan-Meier survival plot depicting progression-free survival according to interim FDG-PET status. (B) Overall survival according to interim FDG-PET status. (C) Progression-free survival according to BCL2 status. (D) Progression-free survival according to BCL6 status. (E) Progression-free survival according to BCL2 and interim FDG-PET negative status. (F) Progression-free survival according to BCL6 and interim FDG-PET negative status.

the time of writing, the relatively short median follow-up, which is much shorter than the expected median survival of the group, means that very few events have occurred that would enable differences to be determined in overall survival. The study demonstrates that immunohistochemical staining for BCL2 enhanced the predictive ability of early interim FDG-PET during chemotherapy. Further larger scale prospective studies

are required to confirm these results, and establish whether the prognostic value of immunohistochemical phenotyping and FDG-PET response-assessment are additive in their ability to predict the prognosis of an individual patient as suggested by this hypothesis generating study.

Paul A. Fields, George Mikhaeel,° Martin Hutchings,° Jon van der Walt,# Tom Nunan,@ Steve A. Schey**

Departments of Haematology and Clinical Oncology,° Pathology,# Clinical PET Center,@ Guy's and St. Thomas' Hospital, London, UK*

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Correspondence: Paul A. Fields, Dept. of Hematology, 4th Floor, Thomas Guy House, Guy's Hospital, London SE1 9RT, UK. Phone: international +44.207.1880141/1431. Fax: international +44.207.1882748.E-mail: paul.fields@gstt.sthames.nhs.uk

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