Controversy II: is interim PET useful in planning treatment for DLBCL?

139 IS INTERIM PET USEFUL IN PLANNING TREATMENT FOR DLBCL?

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Interim-PET performed early during treatment is now considered as one of the most powerful prognostic tools to predict treatment outcome in diffuse large B-cell lymphoma (DLBCL). Some studies have even reported that this prognostic value was independent from IPI or phenotype. However to date, evidence that DLBCL patients benefit from having treatment adapted according to the results of early FDG-PET is based only a limited number of series and conflicting results have been reported. It outlines the need of robust, reproducible and validated criteria for interim PET. International efforts to reach a consensus among experts on recommended criteria for interim-PET reporting are under way. The use of the end treatment criteria appears suboptimal as interim PET explores the kinetic of the tumour destruction under chemotherapy and assesses the chemo sensitivity. Visual qualitative interpretation can vary among observers depending on the reference background used to determine the positivity of a residual activity. The liver has been proposed in a new set of criteria. Moreover it as been proposed that the visual interpretation should be complemented by an SUV analysis of the interim PET using the delta standardized uptake value (SUV) max concept, which decreases the number of false positive results. International Validation Study in DLBCL has been launched to validate the rules proposed by the experts attending the first and the second International Workshop on interim PET in lymphoma held in Deauville and Menton in April 2009 and 2010, respectively. This will be one of the topics of the Third International Workshop, which will be held in September 2011 with the objective to propose shared and validated rules for interim-PET interpretation. Prospective clinical trials aimed at answering the positive role of PET in planning treatment have been launched worldwide and results will be available in the next future. Different therapeutic strategies are being tested, exploring the role of treatment intensification or de-escalation, based on early interim (after 2-3 cycles) PET scan results. The main studies will be presented.

140 INTERIM FDG-PET SCANNING FOR DLBCL SHOULD REMAIN INVESTIGATIONAL

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In 2011, primary therapy for DLBCL incorporates R-CHOP administered in a two or three week schedule. The number of treatment cycles and whether or not consolidation is administered varies between protocols and from country to country. Much of the reported data supporting the use of interim restaging FDG-PET does not include treatment with rituximab-based therapy and at this point is historic in nature; however, nearly all report a negative predictive value (NPV) of greater than 80%. First, in order to be clinically meaningful, the interim FDG-PET scan should reliably identify patients (pts) who will fail standard chemotherapy, and there should be an effective alternative treatment for these individuals. Moreover, the outcome of pts receiving such alternative therapy early should be equal to, or superior to, the outcome of pts receiving the same therapy at the time of clinical treatment failure (i.e. salvage therapy). However, at present there is no clearly established alternative therapy, and the effect of early intervention on pt outcome is unproven.

At MSKCC, we have reported a risk-adapted, phase II study for pts with advanced stage DLBCL. Following induction therapy with four cycles of R-CHOP-14, all pts underwent interim FDG-PET. If the FDG-PET was negative, pts received non–cross-resistant consolidative chemotherapy with three cycles of ICE (ifosfamide, carboplatin, etoposide). Our study is unique in that all pts with a positive interim FDG-PET underwent biopsy of the FDG-positive site; if histopathology showed DLBCL, therapy was changed to 3 cycles of ICE followed by an ASCT. However, if the biopsy was negative pts received three cycles of ICE alone (i.e., the same treatment as the pts with a negative interim FDG-PET). In this study, the NPV of interim PET was > 80%, but the positive predictive value was only 32%. There was no difference in outcome for pts with true-negative and false-positive interim FDG-PET scans, with a 3-year PFS of 80% in both groups. Our results are not at variance with other modern rituximab-based chemotherapy programs for DLBCL. In fact, a number of recent studies using R-CHOP-21, R-ACVBP, R-CHOP-14 or R-EPOCH as primary therapy found a similar false positive rate for interim FDG-PET results as in our report, and there was no difference in PFS between interim FDG-PET positive and FDG-PET negative pts. In addition FDG uptake in residual masses is determined by a number of factors including: the amount of viable tumor cells, number of inflammatory cells, and the degree of FDG retention in them. The contribution by each of these factors may vary with disease (e.g., HL vs. NHL), disease site (e.g., mediastinum vs. abdomen), the treatment regimen, growth factor use, and schedule. Therefore, many questions need to be addressed before a visual cutoff (St Thomas criteria) or number cut-off parameter (delta SUV change) could be accepted in prospective trials as being positive or negative.

Currently based upon available data, we recommend against a change in therapy for patients with DLBCL treated with rituximab-based primary therapy without biopsy confirmation of an abnormal interim FDG-PET scan.