Positron emission tomography scanning: a new paradigm for the management of Hodgkin's lymphoma

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The findings of positron emission tomography (PET), performed very early during ABVD chemotherapy have been proven to be the most important prognostic information for predicting treatment outcome in patients with Hodgkin's lymphoma treated with this chemotherapeutic regimen.[1,2] However, many issues remain controversial, and shared, standard criteria for interpreting PET findings have not yet been determined. It is still unclear, for instance, whether a qualitative approach based on visual assessment should be used, or whether a semi-quantitative approach involving standardized uptake value (SUV) analysis of 2-[^{18}F]fluoro-2-deoxyglucose (FDG) is preferred for PET reporting. In this issue of the Journal, Dann *et al.* propose a new scoring system for the interpretation of interim PET scans in patients with Hodgkin's lymphoma treated with either ABVD or BEACOPP chemotherapy.[3]

Hodgkin's lymphoma is a curable neoplasm given that, after a minimum follow-up of 6 years, more than 90% of patients are still alive and 80% are considered cured.[4] These rewarding results have been obtained by a combination of factors influencing treatment outcome in different ways. These factors can be briefly summarized as: (i) increasing accuracy of staging procedures; (ii) different treatment strategies tailored to well-defined categories of patients with different risks of treatment failure; (iii) the peculiar neoplastic tissue architecture in Hodgkin's lymphoma, which differs from that in more common subtypes of lymphoma such as diffuse large B-cell lymphoma and follicular lymphoma; and (iv) the marked chemosensitivity and radiosensitivity of the tumor. It can be hypothesized that there is a close relationship between the last two factors: indeed, the tumor tissue in Hodgkin's lymphoma is composed of a few, scattered neoplastic cells called Hodgkin and Reed-Sternberg (HRS) cells, accounting for less than 1% of the total cell count found in biopsy specimens, surrounded by a overwhelming population of non-neoplastic mononuclear bystander cells.[5] These latter cells are recruited by chemokines produced by the HRS cells and induce expression of anti-apoptotic proteins in HRS cells and their immortalization via a paracrine loop.[6] The chemokines responsible for recruitment of cells to the microenvironment, thymus and activation-regulated chemokines (TARC-CCL7) and macrophage-derived chemokines (MDC), selectively attract CCR4-expressing cell subsets, including eosinophils, histiocytes, macrophages, plasma cells, and Th2 and Treg lymphocytes, which are all readily detected at tumor sites. There is convincing evidence that forced expression of CCR4 by these various subsets of cells provides the cells with the capacity to migrate along a TARC gradient, so that the function of the CCR4 receptor is not restricted to the subset of T cells on which it is physiologically expressed.[7] These cells are metabolically very active, produce chemokines to recruit new accessory cells and block apoptosis of the HRS.[8] The role of macrophages in recruiting inflammatory cells through chemokines encoded by the genes of the so-called stromal-1 and stromal-2 signature, such as MDC, and the prognostic consequence of this phenomenon have been stressed recently.[9,10]

Chemotherapy is able to switch off the chemokine production of HRS cells, and preliminary observations have shown that serum TARC levels correlate with therapy response in patients with Hodgkin's lymphoma.[11] Another consequence of the characteristic architecture of this lymphoma's neoplastic tissue is the very high overall accuracy of information from interim-PET performed very early during chemotherapy in predicting treatment outcome.[12]

The glucose analog FDG is the most versatile and widely employed PET tracer; its use in Hodgkin's lymphoma imaging is based on Warburg's finding that cancer cells show accelerated glucose metabolism.[13] The surrounding mononuclear cells in Hodgkin's lymphoma cell lines cultured *in vitro* are characterized by very high metabolic activity,[8] and are apparently responsible, *in vivo*, for the FDG uptake in baseline FDG-PET scans. Most patients with Hodgkin's lymphoma show normalization of the FDG-PET scan after two courses of ABVD.[1,2,14,15] However, very similar findings have been reported to be present as early as after a single cycle,[16] or even 7 days after the very first administration of chemotherapy.[17] It appears that both the metabolic activity of the non-neoplastic cells of the microenvironment and chemokine production are shut down after two courses of chemotherapy. This shut down occurs in normal-sized nodes but also in bulky ones, in spite of a persisting mass, as tumor shrinkage takes time and depends on several host factors. The paradoxical phenomenon of a persisting mass without evidence of viable neoplastic tissue has been called "metabolic complete remission".[18,19] This early shut down of chemokine production and metabolic silencing of microenvironmental cells in interim PET-negative cases, as opposed to persisting functional activation of the same cell population in non-responding patients, works as a "power amplifier" for the resolution ability of the PET imaging technique and enables the treatment outcome to be predicted in a "black and white" fashion.

The use of PET for disease status assessment before, during and after therapy in lymphoma as well as in other tumors has increased dramatically during the last few years.[20,21] In Hodgkin's lymphoma, all the above-mentioned clinical applications, as well as the role of PET prior to stem cell transplantation and during follow-up have been extensively investigated and recently reviewed.[22,23] At the moment PET could be considered a routine diagnostic procedure at baseline, at the end of therapy and

before stem cell transplantation; interim-PET, however, should be considered investigational and its use recommended only within clinical trials. Surveillance PET scanning in the follow-up of patients should be discouraged and its use does not seem to be cost-effective (Figure 1).

One of the most popular and widely assessed clinical applications of PET in lymphoma management is the early evaluation of chemosensitivity during conventional ABVD treatment. The information derived from interim FDG-PET, performed after two courses of ABVD, very early in the treatment of Hodgkin's lymphoma, has been proven to be able to predict treatment outcome reliably in more than 90% of patients,[1,2,14,15] with a sensitivity and a specificity in Hodgkin's lymphoma ranging between 43% and 100%, and 67% and 100%, respectively.[25] Based on these results a number of clinical trials have been planned worldwide, aimed at assessing the overall efficacy of flexible chemotherapy adapted according to the results of interim PET performed very early during treatment, both in limited or advanced-stage Hodgkin's lymphoma. Nearly 80% of patients with Hodgkin's lymphoma show a negative PET scan after two courses of ABVD, while in 20% and 9-10% of the patients, the scan is positive or minimally positive, respectively.[1,2,14,15] In the case of a minimally positive PET scan, a persistent faint uptake of FDG is detected, most often in a site where a bulky tumor was recorded at baseline. This area of persisting FDG uptake was first described as minimal residual uptake (MRU) and is defined as low grade uptake of FDG (just above the background level) in a focus within an area of previously noted disease reported by the nuclear medicine physicians as not likely to represent malignancy.[26] The significance of this finding is unknown, but it is probably a consequence of an inflammatory tissue reaction to the cytolytic effect of chemotherapy, leading to non-specific FDG uptake by inflammatory cells infiltrating the neoplastic lesion.[27] Most, if not all, of the reports on interim-PET performed during ABVD chemotherapy in Hodgkin's lymphoma have stressed the good prognosis of patients with a interim scan showing MRU, and concluded that MRU-positive patients should be considered as having early PET-negative scans.[1,2,14,15] However different definitions of MRU have been proposed. In 2007, MRU was defined by Gallamini[14] and Juweid (*personal communication*) as weak, persisting FDG uptake with an intensity equal or slightly superior to that of the mediastinal blood pool structures, while in 2008, the expert nuclear medicine physicians from the PET Center at Guy's and St. Thomas Hospital, London proposed a definition of MRU as residual FDG uptake with an intensity lower than or equal to the one recorded in the liver.[28] The evolution of the concept of MRU in the years immediately following its introduction consisted in a broadening of the boundaries of the area of the MRU itself, with the aim of increasing the specificity and reducing the false positive results of interim PET scan in predicting treatment outcome.[29] The definition of MRU for the purposes of interpreting interim PET scans differs in the various PET-response adapted clinical trials that are currently ongoing worldwide both in early-stage and advanced-stage Hodgkin's lymphoma.

Given the desire to be able to compare results of these trials and the need to establish simple and reproducible rules for interim-PET reporting, an international consensus workshop among nuclear medicine experts and hematologists was held in Deauville in April 2009,[30] and retrospective international validation studies to validate the proposed rules have been launched both in Hodgkin's lymphoma and diffuse large B-cell lymphoma.

Interim PET during BEACOPP chemotherapy has been proposed, and preliminary reports on this strategy have been presented.[31-33] Most reports focused on the very good negative predictive value for treatment outcome, but the specificity and positive predictive value were very low, indicating that the existing interpretation criteria are inadequate. In the present issue of Haematologica, Dann *et al.*[3] propose a new dynamic interpretation score for interim-PET, based on a comparison of interim and baseline scans with a quantitative assessment of the reduction of the intensity and number of residual lesions in the interim scans with respect to those found in the baseline study.[3] Dann *et al.* retrospectively evaluated a cohort of 96 patients with Hodgkin's lymphoma, most of whom (66%) had

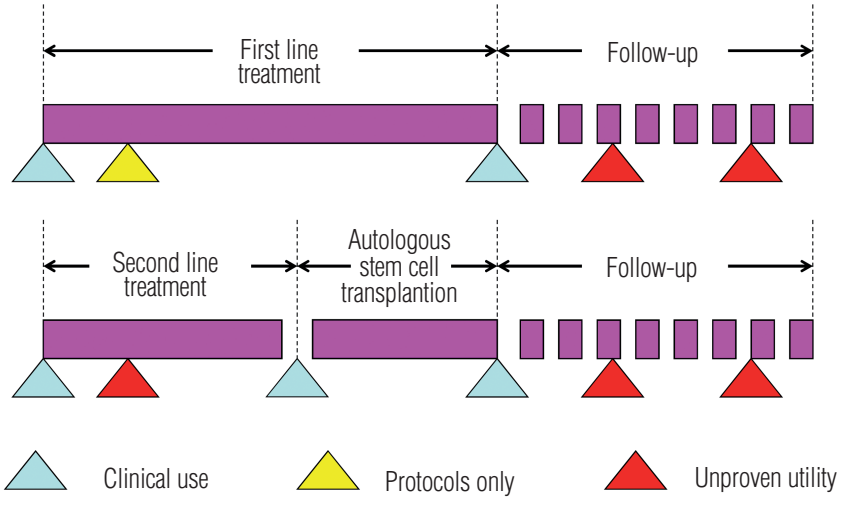

Figure 1. Guidelines for the clinical use of PET in Hodgkin's lymphoma and diffuse large B-cell lymphoma (Adapted from Cheson *et al.*)[24]

advanced stage disease, treated with three different schedules: ABVD, baseline or escalated BEACOPP. Twenty-one percent of the patients treated with ABVD and 27% of those treated with baseline or escalated BEACOPP showed a positive interim PET scan according to static criteria, thus confirming the previous reports of a low specificity of interim PET when interpreted according to classical static criteria. Upon reviewing the interim scans using the proposed dynamic score, the number of positive interim scans fell from 24 to 6; however the overall accuracy of the new score could not be assessed since most patients changed therapy according to interim-PET scan results.

In conclusion, PET is currently the single most powerful prognostic tool for planning treatment in patients with Hodgkin's lymphoma. However, in order to share the responsibility of this assumption with the scientific community, and to propose PET scanning for daily clinical practice outside clinical trials, a major international effort is underway to reach a consensus on definite rules for interpreting interim-PET findings. It is hoped that many of the unsettled issues related to this novel technique will be clarified by the ongoing international validation studies.[30]

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