FDG-PET as a biomarker for early response in diffuse large B-cell lymphoma as well as in Hodgkin lymphoma? Ready for implementation in clinical practice?

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A short history

Major changes have taken place in the staging and response assessment of malignant lymphoma in the last two decades. With the introduction of fluorodeoxyglucose-positron emission tomography (FDG-PET) and positron emission tomography-computed tomography (PET-CT), the criteria for staging and monitoring response have changed dramatically. In the revised Cheson criteria published in 2007,[1] staging with FDG-PET was still optional, and end-of treatment assessment using FDG-PET and CT was obligatory for Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL). In the Lugano criteria published in 2014,[2] PET-CT is recommended for staging as well as response assessment following therapy, as it is the most accurate imaging modality. However, one of the characteristics of (molecular) metabolic imaging is to be able to assess metabolic changes early in treatment. The question arises whether 'interim' FDG-PET-CT (iPET) can be used as a biomarker to differentiate good and poor responders during treatment, in order to modify therapy and to improve outcome. Recent clinical trials have addressed these questions, and we discuss the results and the implications for clinical practice.

Assessment of interim-PET scans

International guidelines recommend the use of a 5-point scale [also called the Deauville score (DS)] for grading FDG-uptake in lymphoma, compared to physiological uptake in the mediastinum and liver, for response assessment in daily practice and clinical trials.[2-4] No FDG uptake is graded as DS 1; uptake less than or equal in intensity to the mediastinum as DS 2; lesions with FDG uptake between mediastinum and liver are assessed as DS 3; uptake more intense than liver is scored as DS 4; and markedly increased uptake or new lymphoma-related lesions as DS 5 (Figure 1). This categorization has a high interobserver agreement in HL and DLBCL.[5,6]

However, FDG-PET is also a quantitative imaging technique, allowing semi-quantitative imaging interpretation, using standardized uptake values (SUV). Reporting change of FDG uptake (usually expressed as a relative change) can also be used for interim response assessment. The reliability of the results depends on having comparable procedures for patient preparation and injection, and scanning and image reconstruction protocols, as well as comparable data analysis. Quality control and quality assurance procedures are also required to maintain the accuracy and precision of quantification. Recently, the European Association of Nuclear Medicine (EANM) guidelines for FDG-PET in tumor imaging for trials and clinical practice have been up-dated,[7] and an accreditation system is available (EARL; *http://earl.eanm.org*). Within clinical studies, these changes in SUV are being compared with visual assessment. Besides SUV, metabolically active tumor volume defined with FDG-PET is being investigated.

Interim-PET in Hodgkin lymphoma

Hodgkin lymphoma is a lymphoma entity with cure rates of up to 90%. iPET predicts response early during treatment and PET-guided therapy is a new strategy in development for HL. The goal of current and recently completed clinical trials is to achieve optimal efficacy in terms of progression-free survival (PFS) and overall survival (OS), and to reduce long-term adverse effects.

The first reports using iPET to de-escalate therapy in responding individuals with early-stage disease have been published. The UK RAPID study[8] and the EORTC H10 study[9] have randomized patients with complete metabolic response (CMR) on iPET after 2-4 cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) treatment to receive radiotherapy (RT) or no further treatment (NFT). Both were non-inferiority studies, with a slightly different design. Involved field was used in RAPID and involved-node RT in H10. RAPID investigators accepted that by abandoning RT some loss of disease control was inevitable, whereas H10 investigators designed their trial to demonstrate that patients could be spared RT without any compromise in disease control. Both studies demonstrated a modest PFS advantage for patients receiving RT (Table 1).

In the RAPID trial, the 3-year PFS was 97.1% using RT *versus* 90.8% for NFT in a *per*-protocol analysis (HR 2.36; 1.13, 4.95). There was no significant difference in 3-year OS: 97.1% (RT) *versus* 99.0% (NFT). In the H10 study, 1-year PFS was 100% (favorable disease) and 97.3% (unfavorable disease) using RT *versus* 94.9% (favorable) and 94.7% (unfavorable) for NFT. The H10 study was halted early for patients with CMR as it was felt unlikely to demonstrate non-inferiority for the NFT option with a 10% decrease in 5-year PFS where the threshold for non-inferiority was set at a hazard ratio of respectively 3.2 and 2.1 for the favorable and unfavorable subgroups. Nonetheless, patients had excellent outcomes in both trials whether or not they received RT. However, follow up in both trials is still short, and (late) adverse effects of radiotherapy may become apparent over time.[10] Results from the HD16 and HD17 tri-

Table 1. Studies with i-PET adapted therapy in Hodgkin lymphoma and diffuse large B-cell lymphoma.

Author/study	Year	Design	Type +stage	Number	i-PET after	Pos criteria	i-PET negative therapy	i-PET positive therapy	Median FUP	Outcome i-PET -/+
HL Radford/ RAPID[8]	2015	RCT	st IA/IIA non-bulky HL	571	3x ABVD	DS 3/4/5	IF RT or NFT	1x ABVD + RT	60 mo	3-yr PFS: IF RT: i-t-t: 94.6% p-p a: 97.1% *vs.* NFT: 90.8%. 3-yr OS: IF RT: 97.1% *vs.* NFT: 99.0%
Raemaekers/ EORTC H10[9]	2014	RCT	st I/II supra-diaphragmatic HL	1137	2x ABVD	IHP	Favorable: 2x ABVD or 1x ABVD+INRT Unfavorable: 4x ABVD or 2xABVD+INRT	Favorable: 2x BEACOPP-esc+ INRT Unfavorable: 2x BEACOPP-esc + INRT	1.1 yr	1-yr PFS fav. IN-RT: 100% NFT 94.9%. 1-yr PFS unfav. IN-RT: 97.3% NFT 94.7%
Press/US Intergroup S0816[11]	2016	phase II	st III/IV HL	336	2x ABVD	DS 4/5	4x ABVD	6x BEACOPP-esc	39.7 mo	2-yr PFS: 82%/64% sign 2-yr OS: 98%
Johnson/ RATHL[12]	2015	RCT	st II-IV HL	1137	2x ABVD	DS 4/5	4x ABVD or 4x AVD	BEACOPP-14 or BEACOPP-esc	32 mo	3-yr PFS: ABVD: 85.5%; AVD: 84.5% / i-PET pos:68% 3-yr OS: ABVD:97.0%; AVD: 97.5% / i-PET pos: 86%
Straus/ CALGB Alliance 50604[20]	2015	phase II	non-bulky st I/II HL	164	2x ABVD	DS 4/5	2x ABVD	2x BEACOPP-esc+ IF RT	2 yr	3-yr PFS: 92%/66% sign
Ganesan[21]	2015	phase II	st IIB/III/IV HL	50	2x ABVD	DS 4/5	2x ABVD	4x BEACOPP-esc	24.7 mo	2-yr EFS: 82%/50% sign
DLBCL										
Hertzberg[22]	2015	phase II	poor risk DLBCL	151	4x R-CHOP14	IHP	2x R-CHOP +2R	3x R-ICE + Z-BEAM ASCT	35 mo	2-yr PFS: 74% /67% NS 2-yr OS: 88%/78% NS
Swinnen/ E3404[23]	2015	phase II	DLBCL st II (bulky)/ III/IV	80	3x R-CHOP	'ECOG criteria'	2x R-CHOP	4th R-CHOP +4x R-ICE	4.6 yr	2-yr PFS: 76% /42% NS 3-yr OS: 93%/69% NS
Stewart[24]	2014	phase II	adv st DLBCL	70	2x R-CHOP21	>Liver at >1 site	4x R-CHOP	1x R-DICEP + R-BEAM ASCT	41 mo	3-yr PFS: 65.2%/52.7% NS 3-yr OS: 68.4%/70.5% NS
Pardal[25]	2014	phase II	DLBCL/ gr 3B FL	71	3x R-MegaCHOP	IHP	3x R-MegaCHOP	2x R-IFE + BEAM ASCT	42.8 mo	3-yr PFS: 81%/57% sign 3-yr OS: 89%/73% NS
Dührsen/ PETAL[19]	2014	RCT	aggressive NHL (~80% DLBCL)	853	2x R-CHOP	<66% ΔSUV reduction	4x R-CHOP or 4x R-CHOP+2R	6x R-CHOP or 6x 'Burkitt protocol'	33 mo	2-yr TTTF: 79% i-PET+/47% i-PET- sign.
Sehn[26]	2014	phase II	adv stage DLBCL/PMBCL	150	4x R-CHOP21	IHP	2x R-CHOP$_{21}$	4x R-ICE (+RT if end of treatment PET pos)	45 mo	4-yr PFS: 91%/59% sign 4-yr OS: 96%/73% sign
Casasnovas[16]	2011	phase II	DLBCL/PMBCL	102	2x R-CHOP14 or 2x R-ACVBP	IHP	R-CHOP14 or MTX+ R-ifos-VP-16 +AraC	MTXiv + Z-BEAM ASCT	19 mo	PET 2: 2-yr PFS 73%/77% NS 2-yr OS 93%/ 84% NS PET 4: 2-yr PFS 81%/73% NS 2-yr OS 94%/83% NS
Moskowitz[14]	2010	prospective	adv stage DLBCL	98	4x R-CHOP14	>local bg	3x ICE	biopsy neg: 3x ICE; biopsy pos:2x ICE+ 1x R-ICE+ASCT	44 mo	PFS NS OS NS
Kasamon[27]	2009	phase II	aggressive B-cell lymphoma	59	2 or 3X (R-)CHOP	> bg	(R-)CHOP14 or 21	2x (R-)ESHAP or 2x R-ICE	33.6 mo	2-yr EFS 89%/75% 3-yr EFS: 82%/65%

HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; NHL: non-Hodgkin lymphoma; iPET: interim positron emission tomography; RCT: randomized clinical trial; phase II: prospective phase II study; st: stage; adv: advanced; gr: grade; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; (R-)CHOP: (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone; R-ACVBP: rituximab, doxorubicin, vindesine, bleomycin, prednisone; DS: Deauville score; IHP: International Harmonization Project; SUV: standardized uptake value; bg: background; rand: randomization; IF RT: involved field radiotherapy; NFT: no further treatment; INRT: involved node radiotherapy; AVD: doxorubicin, vinblastine and dacarbazine; 2R: 2 cycles rituximab; MTX: methotrexate; R-ifos-VP-16: rituximab, ifosfamide, vindesine; AraC: cytosine arabinoside; RT: radiotherapy; (R-)ICE: (rituximab), ifosfamide, carboplatin, etoposide; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; esc: escalated; BEAM: carmustine, etoposide, cytarabine, melphalan; ASCT: autologous stem cell transplantation; R-DICEP: rituximab, dose-intensive cyclophosphamide, etoposide, cisplatin; R-IFE: rituximab, ifosfamide, etoposide; MTXiv: intravenous methotrexate; Z-BEAM: ibritumomab tiuxetan, carmustine, etoposide, cytarabine, melphalan; R-ESHAP: rituximab, etoposide, cisplatin, high-dose cytarabine, methylprednisone; FUP: follow up; mo: months; yr: years; PFS: progression-free survival; i-t-t: intention-to-treat; p-p A: per-protocol analysis; fav.: favorable; unfav.: unfavorable; OS: overall survival; EFS: event-free survival; TTTF: time to treatment failure; NS: not significant; Sign: statistically significant; ECOG: Eastern Cooperative Oncology Group.

als of the German Hodgkin Study Group are currently awaited. Both trials are comparing standard combined modality treatment with a PET-directed regimen, omitting radiotherapy for patients with complete metabolic response after chemotherapy (*www.ghsg.org*).

So de-escalation has become a real option in clinical practice, but requires detailed discussions between patients, hematologists and radiation oncologists. Balancing the risks and benefits of chemotherapy alone *versus* combined modality treatment depends on patient age, fitness, disease distribution and, most importantly, the individual assessment of that risk in the decision-making process.

The recently published US Intergroup Trial of response-adapted therapy for stage III-IV Hodgkin lymphoma used early interim PET after 2 cycles of ABVD to escalate therapy for patients with Deauville score 4 or 5 to BEACOPP escalated. The authors concluded that response-adapted therapy based on iPET imaging seemed promising with a 2-year PFS of 64% for PET2-positive patients compared to historical series with 2-year PFS of 15%-30% for PET-positive patients treated with ABVD.[11]

Unpublished data presented in early and advanced disease from the EORTC H10 and the recently published UK Response Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) studies[12] also suggest that escalation from ABVD to BEACOPP may be beneficial in patients with an inadequate response on iPET after 2 cycles. In RATHL, patients randomized to receive AVD rather than ABVD on the basis of CMR on iPET had less pulmonary toxicity but no significant difference in 3-year PFS/OS. Published data are awaited for the EORTC H10 trial but in the meantime, at least in centers that participated in RATHL, this strategy is being offered to patients in clinical practice.

The H10 and RAPID trials used the mediastinal blood pool (equivalent to DS 2) as the reference region for CMR; the RATHL study used the liver (DS 3). To avoid under-treatment, it may be desirable to use the mediastinal blood pool in trials testing de-escalation. The RATHL study, which tested both treatment escalation and de-escalation, used DS 3 as a cut off for CMR. The liver is a more reliable threshold for reporting iPET with respect to inter-reporter agreement and there was good agreement amongst reporters in local PET centers with expert central reviewers in RATHL.[4] This supports the use of DS 3 for assessment of CMR in patients undergoing standard treatment but, in the authors' opinion, in early stage disease for de-escalation it is still prudent to use DS2. It is imperative that those reporting PET results and clinicians understand how the DS should be used for response-adaptation in clinical practice. Nowadays, many imaging specialists are educated in using DS not only for clinical trials, but also for clinical practice.

Interim-PET in diffuse large B-cell lymphoma

R-CHOP is the standard therapy in DLBCL and will cure approximately 60% of patients. Standard treatment for

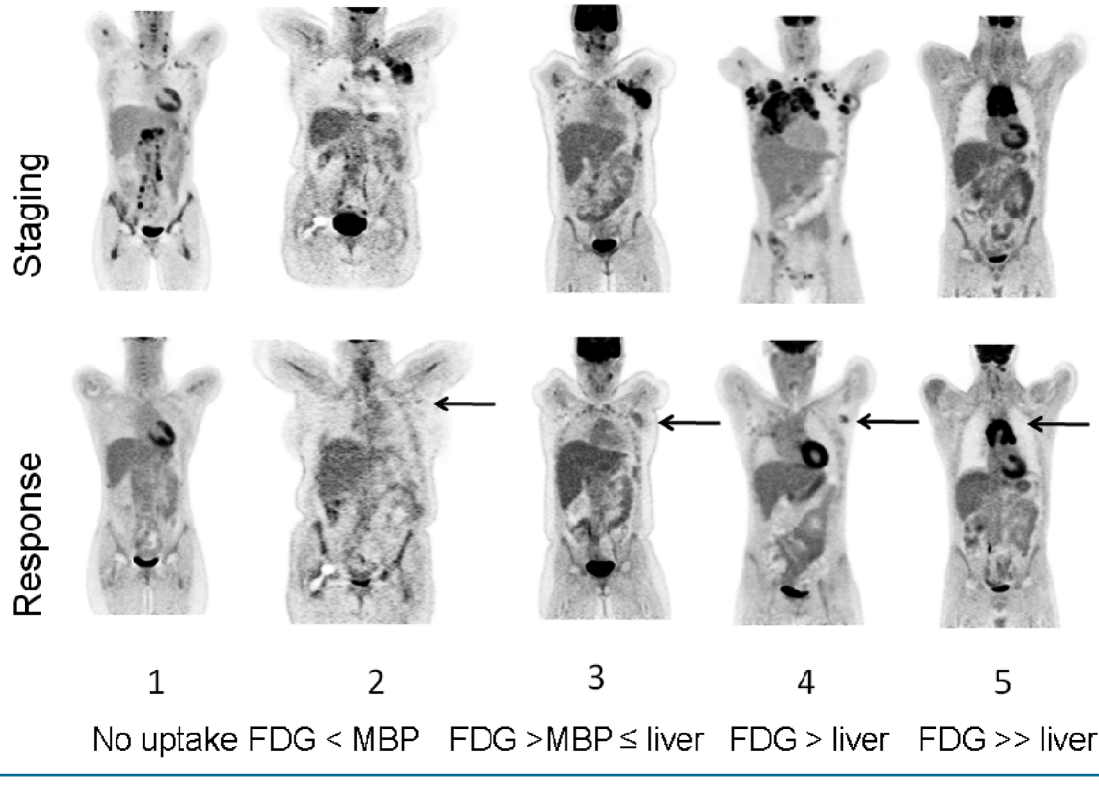

Figure 1. Coronal slices from 5 patients are shown at baseline and response. The level of uptake at residual sites, where present (arrowed) is graded according to the 5-point Deauville score.

the significant proportion of patients up to the age of 70 years with relapsed or refractory disease is platinum-based immunochemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). However, the results of second-line immunochemotherapy are disappointing, especially for patients who relapse within one year of completing R-CHOP treatment.

Early identification of non-responders is of the utmost importance to maximize the chances of successful second-line therapy and to decrease side-effects associated with ineffective first-line therapy.

To distinguish responders from non-responders, observational studies have indicated that iPET may be an effective predictive biomarker of outcome in DLBCL, but there are inconsistencies.[13,14] It is unclear to what extent these are due to differences in the timing of PET during therapy, the choice of therapy and/or different PET reporting criteria. The current recommendation is to use DS, but earlier studies used International Harmonization Project criteria which separated PET into 'positive' and 'negative' by comparing FDG uptake with the intensity of the blood pool or nearby normal structures, if less than 2 cm, to offset partial volume effects.[15]

Standardized uptake value based methods have also been used to assess response in DLBCL. To date, most studies have applied the change in FDG uptake in the pixel with the highest uptake (SUVmax) before and during/after treatment (ΔSUV).[6] Casasnovas *et al.* advocate ΔSUV as the most accurate criterion for response assessment. For lymphomas, in which cure is feasible and a rapid drop in SUV is common, cut offs for a clinically relevant interim assessment of response have been reported to range from 66% to 91%.[16] Finally, metabolic tumor volume at baseline, perhaps combined with iPET response, has recently been reported as demonstrating predictive value.[17]

Currently, an international consortium called PETRA (PET-Re-Analyses) is pooling clinical studies in DLBCL to perform an individual patient data meta-analysis and compare different methods in assessing interim-PET.[18] Hopefully, this will reveal the optimal time point and best visual or semi-quantitative PET-metrics to use for interim assessment.

Another important issue is whether early identification of patients who are likely to be refractory to R-CHOP will result in better outcomes if these patients can be salvaged with high-dose chemotherapy or novel non-chemotherapeutic agents. Progress in targeted therapies in DLBCL might shift treatment paradigms from broad-spectrum poly-chemotherapy towards more targeted therapies based on genetic heterogeneity and complexity. These new drugs are currently being tested within phase I-II trials and results are awaited. Predicting response or resistance to a specific therapy will not only expedite the introduction of the most effective therapy to the patient but will also most likely be necessary to reduce the overall costs.

Nowadays, international guidelines do not recommend changing standard treatment on iPET unless there is clear evidence of progression. Nonetheless, if mid-treatment imaging is performed, PET is better than CT at predicting prognosis and can be useful to exclude the possibility of progression. Preliminary published data and data presented only in abstract form suggest that, for patients with inadequate response on iPET, current chemotherapy-based escalation strategies may not overcome treatment resistance[19,23-24] (Table 1). For these patients, a more effective initial therapy regimen is needed.

Conclusions

FDG-PET is a reliable biomarker for assessing early response in HL. The high negative predictive value of CMR after 2-3 cycles of ABVD has been the basis for recent trials exploring de-escalation of therapy in early-stage disease. The high positive predictive value in advanced disease has also been the focus of clinical trials, with promising data presented for patients escalated from ABVD to BEACOPP if they do not achieve a CMR after 2 cycles. In HL, PET-adapted therapy based on early response is rapidly becoming a clinical reality.

In DLBCL, the ability to escalate treatment early for patients unlikely to respond to first-line immunochemotherapy is highly desirable, as these patients do not have good salvage options. Obtaining a CMR on interim PET has a high negative predictive value, but partial metabolic response is also often associated with good outcomes. Modifying treatment for patients who do not achieve an early CMR in DLBCL is likely to lead to overtreatment of a significant proportion of patients, with associated costs and patient anxiety.[28] Early data suggest that patients with early failure also show treatment resistance with currently available salvage therapies, and novel, more targeted treatment strategies are clearly needed.

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