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Interim FDG-PET does not predict outcome in advanced-stage Hodgkin lymphoma patients treated with BEACOPP

A recent study by Borchmann et al (2018), published in *Lancet*, included 1945 patients with advanced-stage Hodgkin lymphoma whose therapy was adapted on the basis of interim fludeoxyglucose positron emission tomography (FDG-PET) results after 2 cycles of bleomycin, etoposide, doxorubicin, cyclo—phosphamide, vincristine, procarbazine and prednisone in escalated doses (eBEACOPP). FDG-PET scans after 2 cycles of eBEACOPP were considered positive when residual activity at PET was present with an intensity higher than the mediastinal blood pool (i.e. Deauville score ≥3). Patients with positive interim FDG-PET results after 2 cycles of eBEACOPP treated with standard therapy (6× or 8× eBEACOPP) had a 5-year progression-free survival (PFS) of 89.7%, whereas patients with positive interim FDG-PET results treated with intensified therapy (8× eBEACOPP with additional rituximab) had a 5-year PFS of 88.1%. Patients with negative interim FDG-PET results after 2 cycles of eBEACOPP treated with standard therapy (6× or 8× eBEACOPP) had a 5-year PFS of 90.8%, whereas patients with negative interim FDG-PET results treated with de-escalated therapy (4× eBEACOPP) had a 5-year PFS of 92.2%. Borchmann et al (2018) recommended interim FDG-PET-adapted therapy in order to reduce the number of therapy cycles and associated morbidity in patients with negative interim FDG-PET results.

However, this recommendation was not supported by the results of their study. Note that patients with positive and negative interim FDG-PET results had a similar outcome when treated with 6× or 8× BEACOPP (5-year PFS of 89.7% and 90.8%, respectively), and that there was no experimental arm in which treatment de-escalation was applied in patients with positive interim FDG-PET results. Furthermore, as noted by the authors themselves, so far there have been no other studies on treatment adaptation on the basis of interim FDG-PET in patients treated with BEACOPP (Borchmann et al, 2018). The lack of an experimental arm applying treatment de-escalation in patients with positive interim FDG-PET results in the study by Borchmann et al (2018) and the lack of a comparative historical cohort applying treatment de-escalation in patients with positive interim FDG-PET results underlie that no conclusion, even not yet a presumption, can be made on whether treatment de-escalation is more effective in patients with negative versus those with positive interim FDG-PET results. The fact that patients with positive interim FDG-PET scans had a favourable prognosis after standard eBEACOPP therapy (5-year PFS 89.7%) even suggests that treatment de-escalation may also be feasible in this subgroup of patients. It is acknowledged that some retrospective studies (Gallamini et al, 2007, 2014; Agostinelli et al, 2016) have shown patients with advanced-stage Hodgkin lymphoma treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and positive interim FDG-PET results after 2 cycles of chemotherapy to have a dismal prognosis, making treatment de-escalation in FDG-PET positive patients rather counter-intuitive. However, these studies (Gallamini et al, 2007, 2014; Agostinelli et al, 2016) suffered from a major methodological flaw, because in the vast majority of cases, treatment failure was determined by means of follow-up imaging, suggesting disease progression after completion of therapy, and histological confirmation of relapsed disease was scarcely performed. Considering the reported high false-positive rate of follow-up FDG-PET in Hodgkin lymphoma (El-Galaly et al, 2012), the positive predictive value of FDG-PET during ABVD treatment in predicting outcome in advanced-stage Hodgkin lymphoma may have been seriously overestimated by those studies (Gallamini et al, 2007, 2014; Agostinelli et al, 2016). Consequently, whether a positive FDG-PET result after 2 cycles of chemotherapy equals a dismal prognosis remains unproven.

A second important issue to consider is that the histological substrate of a positive interim FDG-PET scan is actually unknown, because studies that performed histological verification of residual FDG-avid lesions in Hodgkin lymphoma are lacking. On the other hand, multiple studies in non-Hodgkin lymphoma that performed tissue sampling of FDG-avid lesions at PET scans performed during treatment showed very high false positive rates (Table I), the vast majority of which were due to therapy-induced inflammatory changes. These results can very likely be extrapolated to Hodgkin lymphoma. Moreover, only 0.1–1.0% of the pathological tissue in Hodgkin lymphoma consists of malignant Reed-Sternberg cells (Pileri et al, 2002) and virtually all FDG-avidity is caused by surrounding inflammatory cells. These theoretical underpinnings underline that relevant numbers of false-positive interim FDG-PET results in Hodgkin lymphoma are not unlikely, and that treatment de-escalation in Hodgkin lymphoma patients with positive interim FDG-PET scans may be feasible as well.
In conclusion, the results of the study by Borchmann et al (2018) do not support interim FDG-PET adapted therapy de-escalation, because an experimental arm applying treatment de-escalation in patients with positive interim FDG-PET results was lacking. The fact that patients with positive and negative interim FDG-PET results had a similar prognosis when standard (6 or 8) eBEACOPP was applied seriously questions whether interim FDG-PET has any role in steering treatment decisions. Finally, the pathological substrate of a positive interim FDG-PET result in Hodgkin lymphoma is currently unknown, and results of studies performing histological verification of FDG-avid lesions in non-Hodgkin lymphoma showed very high false-positive proportion, which may probably be extrapolated to Hodgkin lymphoma as well. Therefore, scientific evidence to promote interim FDG-PET adapted therapy in advanced-stage Hodgkin lymphoma does not exist yet.

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References
Angiogenin-mediated tRNA cleavage as a novel feature of stored red blood cells

Red blood cell (RBC) transfusion is the most common therapeutic procedure in hospitalized patients. RBC units can be refrigerated for up to 42 days and undergo various biochemical and morphological changes during storage (storage lesions) (D’Alessandro et al., 2015). However, the effects of storage on the RBC transcriptome have not been well-studied. While once thought to lack nucleic acids, RBCs actually contain diverse RBC transcriptome (Kannan & Atreya, 2010; Sarachana et al., 2015). During RNA extraction, cel-miR-254 (~18 nt) are indicated by arrows. The remaining tRNA fragment after “miR-720” removal is indicated by arrowhead.

Fig 1. The increase in “miR-720” expression during RBC storage. (A) Heat map of storage-associated changes in miRNAs of red blood cells (RBCs) from three individuals. miRNA ratios were normalized to Day 1 of storage of each individual and arranged by hierarchical clustering. The two upregulated (red) and downregulated (green) miRNAs were further expanded. (B) Validation of the storage-associated “miR-720” increase by quantitative polymerase chain reaction (qPCR) when normalized against spike-ins foreign miRNAs (cel-miR-254 and osa-miR-442) or endogenous miR-222. (C-D) RNA samples from RBC stored for the indicated days were separated by polyacrylamide gel electrophoresis and transferred to small RNA northern blots and probed with (C) miR-720 and (D) tRNA<sub>Thr</sub>(TGT) full-length probes. The bands corresponding to the full-length tRNA and expected “miR-720” band (~18 nt) are indicated by arrows. The remaining tRNA fragment after “miR-720” removal is indicated by arrowhead.