Commentary

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How can we better predict treatment outcomes in classical Hodgkin's lymphoma?

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"The results indicate that response-adapted therapy based on PET-2 results guarantees a PFS, in PET-2 positive patients and in the overall cohort, higher than PFS of historical controls treated with ABVD."

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Classical Hodgkin's lymphoma (cHL) accounts for 10% of all lymphoma diagnosis. The peculiar feature of the disease is the presence of large multinucleated Reed-Sternberg (RS) and mononuclear Hodgkin (H) cells interspersed with a reactive microenvironment (ME) [1]. The latter can represent more than 95% of the entire tumoral mass and consists of T and B lymphocytes, neutrophils, eosinophils, macrophages, plasma cells, mast cells, fibroblasts and vessels [1]. The kind and the quantity of these populations in the inflammatory background determine the distinction of cHL in histological subtypes: nodular sclerosis, mixed cellularity, lymphocyte depleted and lymphocyte rich. RS and H cells, by secreting numerous cytokines, recruit and set the functional status of the immune infiltrates. The complex network of paracrine and direct interactions between neoplastic clone and the ME, generates prosurvival and anti-apoptotic signals in RS and H cells and favors the escape of tumoral cells from immunosurveillance.

After standard chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and radiotherapy when indicated, almost all patients with cHL have a remission; however 30% of advanced stages and 15% of early stages have a relapse after treatment [2]. Early relapse defines a drug resistant subgroup associated to poor prognosis throughout all subsequent treatments. The German Hodgkin Study Group (GHSG) reported a higher efficacy of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (escalated BEACOPP) compared with ABVD in advanced stage cHL; however because of greater toxicity and increased risk of second cancers, the long-term survival of the two protocols resulted not significantly different [3,4]. Therefore accurate prognostication is needed to identify, at time of diagnosis, high-risk patients to be steered toward more intensified therapy and low-risk patients to be considered for treatment reduction to diminish long-term toxic effects. A commonly used tool to stratify patients with advanced-stage cHL is the International Prognostic Score (IPS), a clinical model based on seven clinical parameters associated with a poorer outcome (male sex, age $\geq$45 years, stage IV, albumin $<$40 g/l, white blood cell (WBC) count $\geq 15 \times 10^9$/l, lymphocyte count $<0.6 \times 10^9$/l or 8% of differential, hemoglobin $<10^5$ g/l) [5]. The IPS defines subgroups of patients with 5-year freedom from progression ranging from 62 to 88% and with overall survival ranging from 67 to 98% [5]. However, IPS is not useful in early stages, a significant proportion of patients allocated to the high-risk group achieve durable complete response with the ABVD scheme and moreover, its utility is limited for risk stratification of patients treated with escalated BEACOPP regimen, as the latter was effective across all IPS risk groups. Therefore, many clinicians believe that IPS has a limited clinical value and that is not the best method to select patients who could benefit from a more aggressive treatment. Numerous studies suggested that the interim functional assessment of treatment response by fluorodeoxyglucose (FDG)-PET after two ABVD cycles (PET-2) is the strongest predictor of treatment failure in advanced cHL, proving superior to the IPS [6]. In a retrospective, international, multicenter study carried out by Gallamini *et al.*, the 3-year progression-free survival (PFS) rate was 28% for patients with PET-2 positive scans and 95% for those with a negative interim PET [7]. The efficacy of intensified treatment strategy

adapted on PET-2 results in advanced stage cHL were evaluated in several prospective trials where PET-2 positive patients after two cycles of ABVD were shifted to a escalated BEACOPP regiments while PET-2 negative patients proceeded with the ABVD scheme [8–10]. The results indicate that response-adapted therapy based on PET-2 results guarantees a PFS, in PET-2 positive patients and in the overall cohort, higher than PFS of historical controls treated with ABVD. Furthermore, Johnson P *et al.* demonstrated that, in advanced cHL, omission of bleomycin from the ABVD regimen, after a negative PET-2, reduced incidence of pulmonary toxic effects without a significant lowering of efficacy compared with standard ABVD scheme [11]. However, some warnings limit the use of a PET-2 adapted treatment in patients with cHL: in early-stage disease, the positive predictive value of PET-2 was low, because of the low *a priori* risk of relapse and the high efficacy of radiotherapy in treating patients with this disease and, in advanced-stage disease, the negative predictive value proved suboptimal, because a variable proportion of patients (5–12%), despite a negative PET-2 scan, do have treatment failure [8,12]. The limitations of clinical and PET based models stimulated the development of effective biological prognosticators to be assessed at the time of diagnosis. Many biomarkers were associated with treatment outcome of cHL. The emerging evidence that the dynamics of the ME influence the clinical behavior of the disease makes the immune-infiltrates and the network of interactions they establish with RS and H cells a potential source of new prognosticators. The studies examining the clinical significance of certain T-cell subsets proved sometimes to be poorly concordant or highlighted survival correlates apparently conflicting with cancer biology (e.g., prognostically negative impact of cytotoxic T-cells or favorable outcome of cases with ME enriched in $FOXP3^+$ regulatory T cells) [13]. Gene expression profiling (GEP) recognized a signature of tumor associated macrophages (TAM) being associated with poor prognosis [14]. Steidl C *et al.* using immunohistochemistry (IHC), correlated increased number of $CD68^+$ macrophages with a shorter PFS and with a higher risk of relapse after autologous hematopoietic stem-cell transplantation [14]. The prognostic value of immunohistochemical quantification of TAM exceeded IPS and was validated in the setting of multicenter Phase III randomized controlled clinical trial E2496 [15]. Although not all the case series confirmed the prognostic role of macrophages, several studies suggest that a high number of either $CD68^+$ or $CD163^+$ TAMs is a strong predictor of adverse outcomes in ABVD treated cHL [16]. However, some further work (e.g., standardization of scoring methodologies and markers) seems needed to establish if IHC-based assessment of TAM can be used prospectively to improve prognostic stratification of patients and to plan appropriate therapeutic strategies. Recently, CD68 was indicated to be an important prognostic marker also in a large prospective cohort of patients treated with upfront escalated BEACOPP in a PET-guided strategy [17]. High CD68 expression at diagnosis was associated to a higher probability of PET-2 positive scan and the combination of these two data identified a population of patients with higher risk of treatment failure [17]. This latter finding is in line with a retrospective European multicenter cohort study that showed a complementary role of interim PET and biomarkers in predicting treatment outcome in patients with cHL treated with ABVD [18]. In particular was constructed a model combining the PET-2 scan evaluation with immunohistochemical quantification of $CD68^+$ and $PD1^+$ cells in ME and of STAT1 expression in RS and H cells. Although no other factor was better than a positive interim PET scan in predicting treatment failure, the proposed algorithm correctly reclassified the response to treatment in more than half of patients with treatment failure despite a negative PET-2 scan, thus increasing the negative predictive value of PET-2 [18].

A promising approach is the development of gene expression-based prognostic models with technology platforms working on the highly fragmented RNA extracted from routinely produced formalin-fixed paraffin-embedded tissue. Scott *et al.*, using multiplex digital GEP on the NanoString platform, examined genes associated with outcome or genes representative of ME components that have been previously identified by IHC and GEP [19]. A 23-gene outcome predictor was then generated that exceeded the IPS and CD68 in identifying patients with advanced-stage cHL at increased risk of death when treated with ABVD and Stanford V upfront regimens [19]. Recently, a further prognostic model created by NanoString digital GEP and based on tumor ME biology in relapsed biopsies, predicted post-autologous hematopoietic stem-cell transplantation outcomes in cHL [20].

Other groups tracked inflammatory markers and signaling proteins reflecting tumor biology, the ME and the host response in peripheral blood. Kanakry JA *et al.* showed that, in cHL patients enrolled in the Intergroup E2496 randomized controlled trial, soluble markers, such as TARC/CCL-17 and soluble CD163 (sCD163), were related to tumor burden and active disease [21]. Moreover, they found that CXCL-10/IP10 and sCD163 were associated to inferior FFS and overall survival independent of IPS and treatment [21]. In the study of Romano *et al.*, patients showing high serum level of Arginase-1, an immunosuppressive molecule produced by neutrophils and myeloid-derived suppressor cells, had a shorter PFS and could be used as complementary information together with PET-2 to predict treatment response [22]. The blood-based markers are more practical as readily and serially

obtainable and they can be used to plan the therapeutic strategy as well as to monitor tumor response throughout treatment and patient follow-up.

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