blood commentary

LYMPHOID NEOPLASIA

Comment on Spina et al, page 2413

Liquid biopsy for Hodgkin: a game changer?

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In this issue of *Blood*, Spina et al evaluate the role of circulating tumor DNA (ctDNA) in newly diagnosed and relapsed patients undergoing treatment of classical Hodgkin lymphoma (cHL).[1]

Response to therapy and detection of relapsed disease are typically assessed by computed tomography and fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in aggressive B-cell lymphoma.[2,3] Although helpful, conventional imaging has several limitations, and alternative modalities for disease assessment are needed. Recently, molecular monitoring of disease looking at ctDNA dynamics has been tested, particularly in diffuse large B-cell lymphoma (DLBCL), in which results demonstrate that the kinetics of ctDNA during therapy can predict clinical outcome.[4,5] Additionally, ctDNA monitoring in remission can detect relapse before the onset of radiologically detectable disease. Studies have also shown that genotyping ctDNA through the application of a technology called cancer personalized profiling by deep sequencing has the ability to identify tumor biological factors that underpin genetic heterogeneity of tumors.[6] This is a particularly helpful concept in DLBCL, considering the disease comprises many molecular subtypes and offers the opportunity to noninvasively identify early emergence of resistant mutations to various therapies.[7] In cHL, the role of ctDNA monitoring is not well studied but hypothetically could be very helpful in response assessment particularly. Currently, interim FDG-PET scanning is used alone to identify chemorefractory disease and guide therapy intensification decisions. Although negative interim FDG-PET accurately predicts excellent outcomes, the positive predictive value of this technique is low in this setting and tools such as ctDNA may aid interim response interpretation.[8] Elucidating the molecular heterogeneity and mutational spectrum of cHL has been much more challenging than in DLBCL because of the paucity of neoplastic cells in the infiltrate. Again, genotyping ctDNA represents a potentially interesting approach.

Spina et al report on a retrospective study in which they used a highly sensitive and deep next-generation sequencing ctDNA assay to analyze specimens from both newly diagnosed (80) and relapsed/refractory (32) patients with cHL. First, having demonstrated that ctDNA mirrors the genetics of microdissected Reed-Sternberg cells using cancer personalized profiling by deep sequencing, they assayed ctDNA in 80 newly diagnosed cases to characterize the mutational landscape of cHL. Among their findings was that ~40% of cases had mutations of *STAT6*, with *TNFAIP3* and *ITPKB* being the other most common mutations. Using a probabilistic classifier that was derived from differential gene expression, they compared the ctDNA signatures of cHL, primary mediastinal B-cell lymphoma, and DLBCL; as has already been demonstrated with gene expression profiling of tumors, cHL and primary mediastinal B-cell lymphoma were genetically closely related and cHL and DLBCL were very distinct. In relapsed/refractory cases in which longitudinal ctDNA monitoring was performed, treatment-related clonal evolution was demonstrated with interesting patterns in a small number of patients on immune-checkpoint inhibitors. Finally, in a subset of newly diagnosed patients who received Adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy, a 100-fold fall or 2-log drop in ctDNA following 2 cycles of therapy predicted a significantly better outcome; in addition, ctDNA quantification complemented FDG-PET imaging assessment.

This study is helpful because it establishes that, in patients with cHL, ctDNA can be used as a source of tumor DNA to profile mutations and characterize disease biology. Technically, in cHL, tumor biopsies represent a huge challenge because, first, mediastinal disease is common, is a challenging site to access, and diagnostic biopsies are frequently small core samples. Second, the low representation of tumor cells compared with background cells and high degree of fibrosis in cHL can make diagnostic interpretation exceeding difficult. Hence alternative "liquid" biopsies may be particularly helpful in this disease, with potentially many roles that include guiding therapy escalations and de-escalations and monitoring clonal evolution patterns, particularly in the setting of novel agents.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Cottereau et al, page 2449

Speaking volumes about volumes

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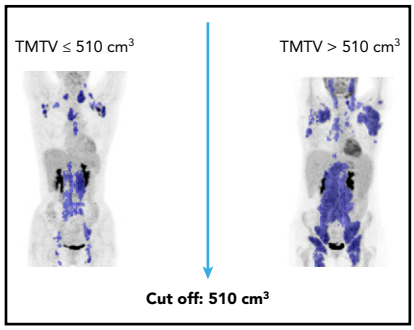
You can only predict things after they have happened.
—Eugene Ionesco

Is that really true? What is clear is that better surrogate end points are needed for follicular lymphoma (FL) clinical trials so we can predict outcomes before they actually occur; to this end, in this issue of *Blood*, Cottereau et al provide valuable direction.[1] FL is the most common of the indolent non-Hodgkin lymphomas.

Whereas a small proportion of patients are likely cured with currently available treatments, the majority experience repeated relapses requiring a succession of therapies. Clinical trials in previously untreated patients relying on overall survival (OS) or progression-free survival (PFS) as primary end points are challenged by the 10 year survival of 80% in these patients[2] resulting in interminable trials such as the recently updated S0016 (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone vs cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone + the radioimmunotherapeutic agent ^{131}I-tositumomab),[2] FOLL05 (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone vs rituximab-fludarabine-mitoxantrone vs rituximab, cyclophosphamide, prednisone, and vincristine),[3] and Primary Rituximab and Maintenance (rituximab-chemotherapy with or without rituximab maintenance) trial[4] having a final analysis being reported out as long as a decade after their initiation. By that time, the clinical questions are often of less interest or irrelevant (radioimmunotherapy is rarely used and ^{131}I-tositumomab is no longer on the market; cyclophosphamide, prednisone, and vincristine and fludarabine are not often the regimens of choice in FL; Primary Rituximab and Maintenance 10-year follow-up data still fail to show a survival benefit for maintenance rituximab). The Follicular Lymphoma Analysis of Surrogate Hypothesis project was created as an attempt to reduce the requisite duration of studies.[5] Using data from 13 randomized trials performed before or following the inclusion of rituximab, complete remission at 30 months was determined to be a strong predictor of outcome. Yet, 2 1/2 years is still a considerable delay in results. Casulo et al[6] conducted a prospective analysis of the National Lymphocare database, which primarily relied on computed tomography (CT) scans, and established progression of disease at 24 months (POD24) as a surrogate, which has been confirmed by other groups. More recently, progression of disease at 12 months has also been suggested as predictive, with patients without an event at that time point experiencing survival consistent with an age-matched population without lymphoma. Indeed, a national US cooperative group trial will be comparing various regimens in the early relapsing population, with correlative studies designed to identify molecular and genetic abnormalities responsible for treatment failure. Although such data will assist in predicting eventual patient outcome, they currently have limited application to the initial management of FL patients. Reeling the surrogate time point back to assessment immediately posttreatment, restaging positron emission tomography (PET)-CT is valuable in predicting PFS and OS either alone or in combination with assays of minimal residual disease, distinguishing high- vs low-risk patients. Unfortunately, no studies to date have demonstrated benefit from reacting to this information.



Examples of TMTV. Figure provided by M. Meignan.

Nevertheless, all of those time points are too little, too late. The Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI-2 (F2) are widely used pretreatment prognostic scores, but fail to provide guidance as to appropriate treatment. Toward this aim, Pastore et al[7] developed the M7 FLIPI score incorporating the mutational status of 7 genes with the FLIPI-2. However, the particularly high-risk subset of patients accounted for but 28% of cases, and did not provide adequate separation of the majority of patients. Meignan et al[8] previously provided evidence that pretreatment total metabolic tumor volume (TMTV) in combination with the FLIPI-2 was able to predict PFS and OS (see figure). In their series of patients with advanced FL, using a TMTV cutoff of 510 cm^3, in combination with an F2 score 3 to 5, the 5-year PFS was 69% for the low-risk group (0 factors), 46% for the intermediate group (1 factor), and 20% for the high-risk group (both factors). In the current manuscript, these same authors extend their observations to incorporate end of