Editorial

A panel of three miRNAs in mycosis fungoides: a new prognostic tool?

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Cutaneous T-cell lymphomas belong to a group of primary T-cell extranodal non-Hodgkin lymphomas. Mycosis fungoides (MF) is the most common subtype (about 50%) and is characterized by quite non-specific erythematous patches in bathing trunk distribution during the early stage. In most of the patients, MF runs an indolent course for decades; however, in about 10% of patients (1), the disease may progress into tumors, expand into the peripheral blood, lymph nodes, and visceral organs (2). A diminished length of survival from diagnosis than what would be expected from their age, disease stage, and other disease characteristics defines the aggressive disease. There are a limited number of prediction models to establish which patient is going to have an aggressive disease. In a recent article published in *Blood*, Lindahl and colleagues (3) have proposed a novel three miRNA classifier system to predict which patients with stage IA-IIA of MF had a higher risk of progressing to stage IIB and above in less than 5 years.

Using miRNA profiling of 384 human miRNAs on formalin fixed paraffin-embedded (FFPE) skin samples, the authors identify that a combination of three miRNAs namely miR-106b-5p, miR-148a-3p and miR-338-3p was the strongest predictor of disease progression. Patients were divided into high- and low-risk groups, and those in the high-risk group had a significantly low progression-free survival (51.4% *vs.* 85.3%, P<0.001) and overall survival (HR, 2.39, P<0.001) compared to the low-risk group. Thirty-three percent patients were found to progress to advanced disease, over a median 2-year period. Interestingly, the authors have measured up their new prognostication tool against recently published Cutaneous Lymphoma International Prognostic index (CLIPi) scores (4) and demonstrated that their panel of three miRNAs was significantly stronger. While miRNA profiling is not something that is routinely performed currently in clinical practice, it may become available as an additional prognostic tool for patients with MF in the near future.

Molecular-based prognostic tests have significantly impacted the classification and management of a number of neoplastic diseases, including breast cancer, uveal myeloma, and thymoma (5-7). The clinical behavior of MF is highly variable and like many other tumors cannot be fully accounted for by traditional staging methods. Some patients with patch and plaque stage will develop distant metastasis and die from their cancer, and conversely, some patients with tumors may be disease free for years (4,8,9). Thus, the development of a highly accurate and robust molecular prognostic test for MF could significantly impact lymphoma management from multiple perspectives. Currently, there are no tests in use clinically to predict the disease course of early-stage MF. Recent attempts to find markers of progression include an examination of genetic, histologic, and cellular factors, which demonstrate an increased expression of Th2 and Th17 cytokines (10) and expression of microRNA processing proteins let-7a and Dicer (11). Elevated serum IgE and large Pautrier's microabscesses have previously been demonstrated as indicators of increased risk for progression and recently reviewed by Dulmage *et al.* (12). We have used proteomic analysis and proposed PARP-1 for differentiating indolent and aggressive MF (13). Despite these studies and a

recent investigation by Lindahl and colleagues (3), definitive markers of progression have yet to be established.

There are some factors have to be taken into consideration for translational studies investigating prognostic biomarkers. Firstly, racial or ethnic background. It remains to be seen whether biomarkers including miRNA expression would differ in racially and ethnically diverse patient populations with different genetic makeup. Secondly, proper choice of healthy controls. Verifying and validating the status of newly discovered biomarkers requires appropriate controls that are frequently omitted in many studies. For example, matched uninvolved skin (3,14), monocytes from healthy volunteers (15), patients' buccal swabs (16), or donor CD4+ cells (17,18) were used in the recent studies investigating genetic biomarkers of diagnosis and prognosis in MF. The use of donor cells or cells of other lineages than lymphocytes is somewhat suboptimal. It is well known that early stage MF has a dominant inflammatory component, which makes it clinically and histologically challenging to distinguish it from other benign inflammatory dermatoses (BIDs) like psoriasis or eczema (19). Due to the difficulty of separating of skin lymphocytes from FFPE samples, many investigators utilize the entire biopsy of skin from patients with early-stage MF, which includes only 15% of malignant cells along with non-malignant inflammatory T-cells, and further, compare the different profile between patients with early MF and age-and-sex-matched healthy controls. Lindahl and colleagues (3) have made use of three miRNAs—miR-106b-5p, miR-148a-3p and miR-338-3p, respectively, which while having prognostic value, are not diagnostic of MF. They can also be seen in various benign BIDs such as psoriasis (20). Ralfkiaer *et al.* (21) proposed that only a few miRNAs were able to distinguish malignant from benign inflammation with high sensitivity, specificity, and accuracy—namely miR-155, miR-203, and miR-205, which does not include any of miRNAs studied by Lindahl and colleagues (3). Sometimes, it is unclear whether biomarkers are being derived from malignant or reactive T-cells, which may confound the results. Besides, the study results may have been different if patients with BIDs were used as the control group instead of healthy individuals.

An important question that remains is which patients with early stage MF would benefit most from miRNA profiling? Should this be done in all patients or can it be targeted to a specific subgroup? Someone may think that the early prediction of the aggressive course of the disease may allow early initiation of more aggressive treatment strategies in patients predicted to be at high risk of progression to advanced MF, while the low-risk patients can be safely monitored without treatment for more extended periods of time. Current treatment recommendations as proposed by the European Organisation for Research and Treatment of Cancer (EORTC) advocate determining treatment protocol by disease stage with skin-directed therapies being first line for early-stage MF, and expectant watchful-waiting for stage IA disease, as these patients might have a normal to almost normal life expectancy, and the potential for long-term toxicity with more aggressive treatment is very high (22). Systemic therapy is recommended only for patients who are refractory or have contraindications to first line therapy. Current guidelines report no survival benefits or improvement in progression-free survival with early initiation of aggressive treatment strategies in early MF and restrict chemotherapy only to advanced disease (23).

miRNA profiling proposed by Lindahl and colleagues (3) depends on accurate assessment of miRNA profiles in human samples. Some of the significant obstacles in this regard include convenience, cost, technical challenges, and the establishment of a standard miRNA sampling technique to minimize inter-laboratory error. The process is labor-intensive, and the molecular targets of various miRNAs as well as their role in multiple cellular pathways, are still under investigation (24,25).

In spite of all those obstacles, we believe Lindahl and colleagues have developed a novel and promising prognostic tool for early-stage MF using a three-miRNA classifier system. Although, this miRNA classifier has the potential to risk-stratify patients based on the likelihood of disease progression and influence treatment decisions, some questions raised above need to be kept in mind before it can be translated into clinical practice.

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Footnote

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