MLL News

4/22/2021

New panel for clarifying unclear erythrocytosis/polyglobulia

An issue that is commonly addressed in our submissions is unclear polyglobulia/erythrocytoses after exclusion of a *JAK2* mutation, the marker lesion for polycythemia vera (PV). However, PV is only rarely diagnosed in *JAK2* negative patients upon bone marrow histology.

If, after molecular genetic and histological exclusion of PV in the clinical and anamnestic context, there is no appropriate cause for a possibly secondary polyglobulia, the case remains unclarified. Regarding a differential diagnosis, we have so far been able to offer a molecular genetic clarification of a familial erythrocytosis, but this diagnosis can also only be extremely rarely confirmed.

The publication by Wouters et al. in *Blood Advances* (2020), in which a subcohort of 133 individuals with erythrocytosis (according to the stricter WHO criteria of 2008, i.e. with Hb > 18.5 g/dl or Hct > 52% in men or with Hb > 16.5 g/dl or Hct > 48% in women) was investigated from the large-scale population-based Dutch lifeline cohort. In the molecular genetic investigation, evidence of clonal hematopoiesis was found in 51 of 133 individuals (38%). A *JAK2* mutation characteristic of polycythemia vera was present, however, in only 7 of 133 (5.3%) cases. Other mutated genes were mainly *BCOR/BCORL1* (16%), *DNMT3A* (14%), *TP53* (10%), *TET2* (6%) and *ASXL1* (5%), and to a lesser extent also *RUNX1*, *CALR*, *CSF3R*, *SF3B1*, *EZH2* and *NRAS*. While cases with a *JAK2* mutation all also showed accompanying leukocytosis or thrombocytosis, all other mutations were also found in cases with isolated erythrocytosis. The common feature of the entire subcohort of clonal erythrocytoses was an association with increased cardiovascular mortality (hazard ratio 2.2).

On the basis of these new data and the demonstrated clinical relevance, an expanded molecular genetic clarification of *JAK2*-negative erythrocytoses appears promising. This is why we have expanded our range of examinations to include a new panel “JAK-negative erythrocytosis/polyglobulia” (see our current examination order or our digital order entry system).

Incidentally: another addition to our range of examinations concerns NK cell neoplasias. It is difficult to distinguish these from reactive changes. In around 30% of cases, this is achieved by detecting a mutation in a gene involved in the *JAK/STAT* signaling pathway (especially *STAT3*). From our research cohort of 5,500 genomes, a previously unknown mutation in the *CCL22* gene was detected in the 63 cases with NK cell neoplasias examined at a rate of 22% (exclusively in *STAT3*-unmutated cases), the functional relevance of which might then be demonstrated in the murine model. These new findings were raised in collaboration with Charles Mullighan’s group at St. Jude Children’s Research Hospital in Memphis. A manuscript is currently undergoing peer review.

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Advances in the targeted therapy of lymphoma

The therapeutic landscape for lymphoma diseases has changed considerably in recent years due to our progress in understanding their pathogenesis. A major advantage has been to reduce the need for chemotherapy and to be able to use new types of targeted therapies alone or in combination. In this newsletter we report in particular on *BCL2* inhibition and its resistance mechanisms, as well as the role of the *MYD88* mutation as well as the *CXCR4* mutation in Waldenström's disease.

With the BTK inhibitor ibrutinib, the *BCL2* inhibitor venetoclax and the PI3Kdelta inhibitor idelalisib, three targeted drugs are now available for patients with lymphoma diseases. Chronic lymphocytic leukemia (CLL) in particular is a pioneer disease for the use of these therapies. With this condition, new points of attack for lymphoma therapies were discovered before they were applied to other pathological entities. Several studies have shown the significant advantage of targeted therapies in combination with a CD20 antibody, as a triple combination with chemotherapy or as a monotherapy (RESONATE-1, HELIOS, Murano study), compared to conventional salvage therapy, particularly in the case of progression, refractoriness or early relapse. Patients with evidence of a del(17)(p13) as well as a *TP53* mutation benefit almost to the same extent as patients without this risk factor. The same applies to patients with an unmutated IGHV status or evidence of a complex karyotype. Such subgroup analyses in particular have revealed the relevance of genetic examinations already at the initial diagnosis. On the basis of these results, conventional immunochemotherapy is now only considered in first-line CLL therapy for patients without these risk factors (Onkopedia guideline CLL 2020). For first-line therapy, the second generation inhibitor of Bruton's tyrosine kinase (BTK) acalabrutinib was approved by the European Medicines Agency (EMA) in the summer of 2020 as another potent oral therapy (ELEVATE-TN study). As is already known from tyrosine kinases, specific resistance mutations (in *BTK*, *PLCG2* or *BCL2*) can appear after therapy with *BTK* or *BCL2* inhibitors, the presence of which makes the continuation of the

corresponding therapy seem almost pointless. For these issues, the MLL offers genetic examinations as well as mutation and resistance tests to better assess any continuation of therapy.

The *MYD88*^{L265P} mutation plays an important role in lymphoplasmocytic lymphoma. It is found in 90% of patients with this pathological entity. The simultaneous presence of a *CXCR4* mutation results in a poorer response to BTK inhibitors, which is why both mutations should be determined before starting any therapy (Treon S.P., Tripsas C.K., Meid K. et al.: *Ibrutinib in previously treated Waldenstrom's macroglobulinemia*. N Engl J Med. (2015) 372(15): 1430–1440). Furthermore, the combination of both mutations encourages interleukin-1 receptor-associated kinases (IRAK) and BTKs to activate oncogenic factors during the development of malignant lymphomas.

In summary, targeted drugs have become indispensable in the therapeutic landscape for lymphoma diseases. The BTK inhibitor ibrutinib is already approved for refractory and relapsed mantle cell lymphoma (MCL) and the PI3Kdelta inhibitor idelalisib is approved for refractory follicular lymphoma. It is to be expected that, in the future, targeted therapeutic approaches will accompany or completely replace conventional chemotherapies even with other lymphomas.

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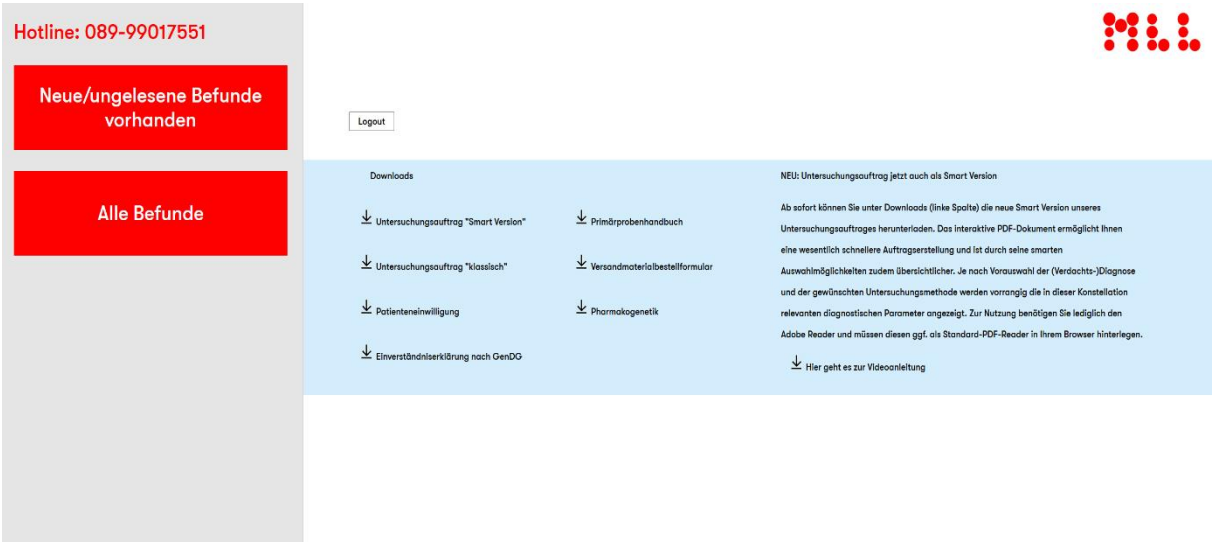

MLL findings portal: Here you can view your findings online

The daily work of doctors, scientists, and medical technicians is becoming more and more digital. A transmission of findings via fax can barely be combined with modern and innovative work processes any more. In addition, technical problems are making their reception more and more difficult. For more than a year now, the web-based **Findings Portal** of the MLL has been used extensively and increasingly for submitting findings, whereby all the findings are then available for download as PDF documents. The feedback from previous portal users has also been extremely positive.

In the MLL findings portal, we make all findings from your clinic/practice (since 2017) available to you digitally and up-to-date to the minute. New or older findings can be opened and downloaded with just a few clicks – anytime and anywhere. In addition, if required, an info email can be sent as soon as a new finding is available. Of course, with the MLL findings portal, all relevant data security standards, including new data protection requirements according to the GDPR, are complied with.

You can register using the registration request on the MLL website or by contacting us directly (by phone on +49 (0)89 99017-551, or by email at befundportal@mll.com). Your user name and the data protection conditions/terms and conditions will then first be sent via email. After you have provided your written consent and sent it back to us by email, fax or land mail, you will then receive a password separately by land mail, which you must then change after you log in for the first time. There is also a procedure in the event of any password loss or misuse. We would be happy to support you in setting up and handling the findings portal.

With our findings portal, we can avoid any technical bottlenecks in the transmission of findings to you and also considerably simplify the querying of any older findings. This is because our desire is to provide you with a completely digital and uncomplicated management system for findings and documentation.

For questions or further suggestions, please contact us by phone on +49 (0)89 99017-551 (contact person: Julia Hennig) or by email at befundportal@mll.com. And did you know that it is now also possible to order sample material online? You can find all further information here.

At this point we would also like to refer you to our digital order entry portal for order entry. For further information on registration and handling, do not hesitate to contact us using the contact details above.

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