Highlights in myelodysplastic syndromes and myeloproliferative neoplasms

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Myelodysplastic syndromes (MDS)

In lower risk MDS, cytopaenias are the principle cause of morbidity and mortality. Despite the fact that erythropoiesis stimulating agents (ESAs) are recommended for the treatment of MDS patients with IPSS low and intermediate I (int-I) risk score suffering from anaemia, these agents are not approved in many countries, due to the lack of phase 3 trials. During EHA 2016, two trials filling in this gap were reported.[1,2] Uwe Platzbecker presented the results of the ARCADE trail, a phase III randomised placebo-controlled, double-blind trial of darbopoietin alfa in low and int-I risk MDS.[1] A total of 149 patients from nine European countries with Hb <10 g/dL, EPO levels ≤500 mU/mL and low transfusion burden were randomised 2:1 to receive 500 μg of darbopoietin every 3 weeks or placebo for 24 weeks. Transfusion incidence was significantly lower with darbopoietin (36.1%) than with placebo (59.2%) (p= 0.008). Best responses were noted in patients with EPO <100 mU/mL. No new safety signals were detected, but fatigue was more frequent in the darbopoietin arm. In 81% of patients, the treatment interval had to be reduced from three to two weeks. In the discussion, the author admitted that the trial was not optimally designed, because of the low dose of darbopoietin and the large number of transfusion independent patients included in the trial. In the open label extension, the dose of darbopoietin was increased in most patients, which resulted in better responses. In a poster presentation, *Fenaux et al.* reported the results of a phase III randomised placebo-controlled, double-blind trial of epoetin-alfa or placebo for 24 weeks in lower risk MDS patients with anaemia.[2] Inclusion criteria were the same as in the ARCADE trial. Epoetin-alfa dose was 450 IU/kg (max 40.000 IU) once weekly. Dose increase to 1050 IU/kg (max 80.000 IU) or dose reduction were driven by weekly haemoglobin (Hb) counts. In total, 130 patients were randomised 2:1. Within eight weeks prior to baseline, 51.8% of epoetin-alfa patients needed transfusions and this was reduced to 24.7% by 24 weeks. A significant improvement in quality of life was reported in the epoetin-alfa arm. There was no difference in drug discontinuation due to AE, drug related thrombo-embolic events or progression to AML between the epoetin-alfa arm and placebo.[2] Hopefully these trials will convince regulatory instances to approve ESA's in lower risk MDS.

A promising new drug is Luspatercept (ACE-536), developed for the treatment of anaemia in lower-risk MDS, especially in patients with ringsideroblasts (RS). Luspatercept has an impact on the biological characteristics of MDS with RS, as it acts as a trap for TGF-β family ligands. These are myelosuppressive cytokines, implicated in the haematopoietic suppression in MDS via overactivation of the SMAD2/3 pathway. Luspatercept reverses the suppressive effects of TGF-β on haematopoiesis, which are upregulated in MDS. By inhibition of the inhibitory pathways on the EPO-receptor, luspatercept promotes late stage erythroid differentiation and increases red blood cell production.

The PACE study is an ongoing phase 2 multi-centre open-label dose-finding study, designed to evaluate the efficacy and safety of luspatercept, administered SC every three weeks, in 58 patients, ESA refractory or EPO >500, of which 82% had ringsideroblasts (RS) (19% RARS, 50% RCMD-RS).[3] The mean Hb level at entry was 8.7 g/dL. In total, 39% of patients had a high trans-

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fusion burden (≥4U/8weeks) and 66% had prior ESA. Transfusion independence was obtained in 42% in the extension study (up to 50+ weeks), which implicates a major improvement in the treatment of these patients. RS and lower EPO levels were predictors of response, but 31% of patients with EPO >500 still responded. Forty-six percent of patients refractory to ESA and 60% of SF3B1 patients (correlating with RS) responded. AE's were mostly grade 1; muscle pain was most prominent. Responses were robust and sustained. Of note, white blood cell counts also increased in many patients.[3] The 2-year extension study is still ongoing, as well as a phase 3 study MEDALIST in regularly transfused patients with lower risk MDS and RS.

In high risk MDS, only half of patients treated with 5-azacitidine (AZA) respond to therapy and the response is rarely sustained. *Unnikrishnan et al.* presented the results of an Australian study on the bone marrow of eighteen patients, ten responders and eight non-responders, investigating the molecular basis of poor response to AZA. Pre-treatment RNA sequencing data revealed an upregulated expression of cell cycle genes and inflammation associated pathways in responders, compared to non-responders. Haematopoietic progenitor cells of non-responders appeared to be more quiescent. AZA could not eliminate founder clones driving haematopoiesis, even in responders.[4]

Finally, *Mittelman et al.* presented the results of the ASPIRE study, a phase II trial investigating eltrombopag in advanced MDS or AML with severe thrombocytopaenia. Unfortunately the patient characteristics (more than 10% blasts or AML, low ECOG, ineligible for intensive therapy) already implicated a dismal prognosis. Therefore, it was not surprising that the results were disappointing, with half of patients dropping out because of side-effects and even more deaths in the investigational arm (36% versus 28%) due to infections, sepsis, cardiac disease and disease progression. Fatigue was more frequent in the eltrombopag arm (25% versus 9%). There was no difference in OS, but survival was limited to only four months in both groups.[5]

Chronic myeloid leukaemia (CML)

Whether tyrosine kinase inhibitor (TKI) treatment can be stopped outside clinical trials or not, was a matter of debate at the last EHA meeting. Today more than 2,000 patients are enrolled in stopping trials. A major complicating factor in interpreting the results of these trials is the variation in stopping criteria in the different trials (e.g. TKI used, duration of treatment, duration of molecular response and depth of response).

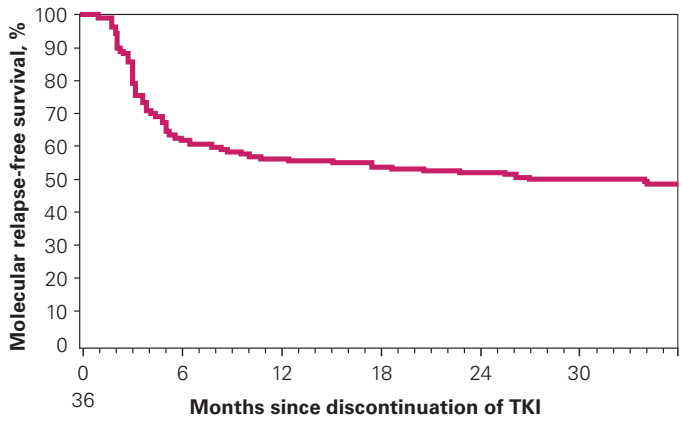
During the presidential symposium, results of the EURO-SKI (European stop TKI study) trial were presented. The EURO-SKI study was set up to define prognostic markers to increase the number of patients in durable deep MR after stopping TKI.[6]

From June 2012 to December 2014, 772 eligible patients in chronic phase (CP) CML from 11 countries and 61 centres were included. Inclusion criteria in the trial were a minimum of three years of TKI treatment (with a long median duration of 7.6 years) and a stable MR4 for at least twelve months (with a median duration of 4.7 years) confirmed by three consecutive PCR results during twelve months prior to inclusion. Ten percent and 18% of patients were high-risk according to EUTOS and Sokal Score, respectively. Patients with a prior TKI failure were excluded. Eleven percent of patients received previous interferon (IFN). Ninety-four percent of patients were treated with imatinib (IM), 2% with dasatinib (DAS) and 4% with nitlotinib (NIL). The primary endpoint, molecular relapse-free survival after stopping TKI, was defined as survival without loss of major molecular remission (MMR).[6]

Treatment-free molecular remission (TFR) at 6 months after cessation was 62%, at 12 months 56%, at 24 months 51% and at 36 months 49% (*Figure 1*). Statistically confirmed prognostic variables on molecular relapse-free survival up to six months were: duration of TKI treatment and duration of MR4. One year of extra TKI treatment increased the chance of TFR with 16% (i.e. odds ratio 1.16). In 30% of patients withdrawal symptoms were reported, consisting of muscle and jaw pain, for which corticosteroid therapy worked well.[6]

In the EURO-SKI trial, more than 80% of relapsed and rechallenged patients already achieved a second molecular remission, but the study is still ongoing, with a planned follow-up at three years. A Nordic sub-study of the EURO-SKI trial demonstrated the prognostic relevance of NK cell number and NK cell phenotype in successful treatment cessation: CD157 NK cell numbers are higher and CD56 NK cell numbers are lower in successfully stopped patients.[6]

In other sessions at EHA, the parameters, important to evaluate when considering to stop TKI treatment were discussed: chronic phase CML, classical BCR-ABL transcript, first line treatment or second line for intolerance (not failure!), duration of TKI (dependent on type of TKI?), level of molecular remission, duration of deep molecular response before cessation, frequency of monitoring (1x/month for six months), previous IFN, trigger



Month	MolRFS %	95%-CI
6	62	59-67
12	56	52-59
24	52	48-56
36	49	44-53

Events:
Molecular relapse n= 348
Death in remission n=5

For patients who resumed treatment, median time to restart was 4.1 months

Figure 1. Molecular relapse-free survival in the EURO-SKI trial.[6]

to restart in case of molecular relapse. An important observation in stopping trials is that late relapses do exist, so careful follow-up is warranted in all CML patients, whether they have stopped treatment or not. Approximately nine hundred patients are currently registered in the 'Polish Adult Leukemia Group imatinib generics registry'. Results on 501 evaluable patients were reported at EHA 2016. One group of patients (40 patients) were treated de novo with generics, a second group (461 patients) was switched from glivec to a generic during a one year therapy period. The two tested generics, Meaxin and Nibix, were no less effective than Glivec and had a comparable safety profile. No increased switching rate between first and second generation TKI was reported.[7]

Treatment with nilotinib (NIL) is associated with an increased risk of cardiovascular disease, with a higher incidence in ischaemic heart disease, cerebrovascular and peripheral vascular disease, especially in the presence of pre-existing risk factors such as hypertension, smoking and hypercholesterolaemia. In the multi-centre ENIGMA 2 study, oral glucose tolerance test, fasting insulin, glucose, adiponectin and serum lipid concentration were measured before the start of TKI and after three and twelve months of treatment in 48 patients on NIL compared to 24 patients on IM and 15 patients on DAS. A fast development of peripheral insulin resistance, with significant hyperinsulinaemia, hyperglycaemia and increased LDL cholesterol, was reported after three months of NIL treatment. This was not the case for patients treated with IM or DAS. Serum adiponectin concentration (an insulin sensitiser) was increased in patients under IM treatment. This declined after discontinuation of IM and switch to NIL.[8]

PV-ET-PMF

The final long-term efficacy and safety results after five years of ruxolitinib in COMFORT-I were presented.[9] In COMFORT-I, 309 patients with myelofibrosis (MF) were randomised (1:1) to ruxolitinib (RUX) or placebo (PBO). RUX starting dose was based on baseline platelet count. A crossover to RUX was allowed after the primary analysis or at any time if they had specified worsening of splenomegaly. The primary endpoint of the study was the proportion of patients achieving ≥35% reduction in spleen volume at 24 weeks. At week 24, patients originally randomised to RUX had a mean reduction in spleen volume of 31.6% and this response was durable with still 18.5% of patients with a ≥35% reduction in spleen volume from baseline at 264 weeks. Median duration of spleen response was 168.3 weeks. More importantly, the OS favoured RUX (HR: 0.69; p=0.025), with 69 deaths among patients originally randomised to RUX versus to 82 with PBO. The median OS has not been reached for patients in the RUX group, as compared to approximately 200 weeks for PBO patients. Mean haemoglobin and platelet count decreased through the first three months, but then gradually increased toward baseline to remain stable from week 24 through five years. The rate of leukaemic

transformation was not increased by RUX.[9] In their final conclusion, the authors stated that the hazard ratio for OS favoured patients treated with RUX and spleen volume reductions were sustained with long-term therapy, demonstrating efficacy and long-term safety of RUX in patients with MF.

JAK2, CALR and *MPL* mutations are mutually exclusive in myeloproliferative neoplasms, suggesting a common oncogenic pathway. The role of *CALR* mutations in megakaryocytic differentiation and oncogenic transformation remains yet to to be elucidated. At the last EHA, a Japanese study in UT-7/TPO cell lines, was presented, demonstrating that mutant *CALR* induced TPO-independent growth and that c-MPL was required for this cytokine-independent growth. Mutant *CALR* 'mimics' TPO by preferentially associating with c-MPL that is bound to JAK2, inducing the phosphorylation of JAK2 and its downstream signaling molecules. This induction was blocked by adding a JAK2 inhibitor to the cell cultures.[10]

Landtblom et al. reported the results of a study performed at the Karolinska in Stockholm, investigating the risk of secondary malignancies in 9,379 MPN patients, compared to 35,682 matched controls.[11] The overall risk of non-haematologic cancer was increased with a hazard ratio (HR) of 1.6. The greatest risk was observed for non-melanoma skin cancer (HR: 2.92), malignant melanoma (HR: 1.85), kidney cancer (HR: 2.85), brain cancer (HR: 2.6) and thyroid cancer (HR: 2.41). Lung cancers, cancers of the GI tract and head and neck tumours were also more frequent in MPN patients. The risk of developing a second haematologic malignancy was also increased with a HR for lymphoproliferative malignancies of 2.62 and for AML 44.04. With the risk of both haematologic and non-haematologic malignancies being increased in MPN patients, the authors advise clinicians to increase their awareness and to provide adequate attention to new symptoms in MPN patients.[11]

Finally, a large study from the European LeukemiaNet, investigating pregnancy outcomes in patients with polycythaemia vera (PV) was also presented at the last EHA meeting.[12] In total, 121 pregnancies in 48 patients were evaluated. Patients were categorised in two groups: group 1 consisted of patients with a pregnancy before the (new) diagnosis of PV (N= 39) and patients in group 2 had a known diagnosis of PV before the pregnancy (N= 82). In group 2, most patients were treated with low dose aspirin and LMWH until six weeks postpartum. The target haematocrit was 40% during pregnancy and phlebotomies were performed if needed (mostly during the first trimester only). A major difference in life birth was noted between the two groups: 77% in group 2 versus 49% in group 1. This was the result of a higher rate of spontaneous abortions (23% in group 1 versus 17% in group 2), stillbirths (21% versus 4%) and foetal losses (8% versus 0%) in group 1. IFN-alpha was used in twelve high-risk patients with 83% live births. The rate of thromboembolic events was similar in both groups, indicating that treatment with aspirin and LMWH could not prevent this complication. The bleeding rate, however, was significantly higher in group 2 (p= 0.036).[12] In conclusion, the high success rate of live birth is encouraging, but comes at a cost of an increased bleeding risk due to treatment of PV patients during pregnancy.

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