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Disease-modifying activity of ruxolitinib in a patient with JAK2-negative CMML-2

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Chronic myelomonocytic leukemia (CMML) is classified by the WHO as an overlap syndrome of myelodysplastic syndrome and myeloproliferative neoplasia (MDS/MPN) because it shares features of both entities.\(^1\) Based on blast percentage in the bone marrow and peripheral blood, CMML is divided into two subtypes. CMML-1 is defined by peripheral blasts <5%, bone marrow blasts <10%, and has an 18% probability to progress to AML within 5 years. CMML-2 in contrast, defined by peripheral blasts of 5–19% and bone marrow blasts of 10–19% (or the presence of Auer rods irrespective of the blast count), has a 63% 5-year risk of AML transformation and hence a worse prognosis.\(^2\) Other prognostic factors are performance status, age, hemoglobin (Hb), platelet and white blood count, transfusion dependence and cytogenetic features.\(^2\) Most patients do not harbor MPN-associated mutations like JAK2-V617F but display alterations in other genes, such as SRSF2, TET2, ASXL1, while only ASXL1-mutations are independently prognostic and are associated with a worse outcome.\(^3,4\) with an incidence of less than 1 in 100,000 CMML being rare.\(^5\) A standard therapeutic regimen is lacking at present as CMML is mostly investigated as a subtype of MDS trials.\(^2\) As allogeneic hematopoietic stem cell transplantation is the only curative treatment, with a high associated mortality, current therapeutic approaches are mainly symptom-based and consequently start with disease-related complications such as worsening cytopenia, increasing blood counts, infections or progressive transfusion dependency.\(^2\) Cytoreductive chemotherapy is used in the case of leukocytosis and hypomethylating agents can improve cytopenias when transfusions and growth factors are insufficient.\(^6\) The main problem in the use of classical chemotherapy is the associated toxicity. Thus, the goal of current research is to identify targeted therapies to minimize potential drug-associated side effects.

Ruxolitinib is a janus kinase 1/2 (JAK1/2) tyrosine kinase inhibitor and is approved for the treatment of myelofibrosis (MF) and polycythemia vera (PV). The JAK-STAT pathways are essential for the signal transduction of proinflammatory cytokines, which are thought to be mediators of B-symptoms, fatigue, weakness, abdominal and bone pain, cachexia, and pruritus.\(^7\) Ruxolitinib decreases circulating cytokines \(^7,8\) and pivotal studies have demonstrated its impressive capacity to reduce disease-related symptoms as well as spleen volume in MPN as MF, PV and essential thrombocythemia.\(^7–11\) Recently a phase-1 study by Padron et al. demonstrated symptomatic benefit and good tolerability of the agent in the setting of CMML-1.\(^5\) Here, we present the first use of ruxolitinib in a patient with CMML-2, which was associated with symptomatic relief and reduction of blast percentage in the bone marrow.

A 64-year-old man presented with night sweats and severe fatigue accompanied with a susceptibility to airway infections for 3 months. The symptoms were collected with the aid of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30). Apart from a persistent (>2 years) peripheral monocytosis, the blood count was normal. Ultra sound revealed a slight splenomegaly (13 cm). To specify the monocytosis, a bone marrow examination (BME) was performed. Morphological and cytochemical analyses revealed hypercellularity, multilineage dysplasia (erythroid-, granulo-, megakaryo- and monopoiesis), increased monocytes (14%), and 14% blasts. The karyotype was unremarkable and BCR-ABL1 fusion gene was ruled out by PCR. Thereupon a CMML-2 was diagnosed. As certain gene mutations are associated with CMML,\(^3\) we sequenced the bone marrow specimen and detected one mutation in the SRSF2 gene (c.284C > G) with a variant allele frequency (VAF) of 6% and 2 mutations in TET2 (c.4546C > T, c.4043A > G) with VAF of 40% and 29% (mutations are based on Ensembl Transcript IDs, Ensembl release 74: Dec 2013: ENST00000380013 for TET2
and ENST00000392485 for SRSF2). No mutations of JAK2-V617F, ASXL1, MPL and CALR were present.

According to the Global MD Anderson Scoring System,[2] the patient had low risk. In the absence of leukocytosis and cytopenias, the use of cytoreductive or hypomethylating agents did not seem justified. As fatigue and night sweats caused a high level of discomfort to the patient, an off-label use of ruxolitinib was suggested and approved by the insurance company. The starting dose of 15 mg twice-daily was reduced to two times 10 mg after 16 weeks because of a hemoglobin decrease from 14.0 to 11.3 g/dl. Afterwards the anemia improved to 12.6 g/dl, 16 weeks because of a hemoglobin decrease from 14.0 to 11.3 g/dl. Afterwards the anemia improved to 12.6 g/dl, which was tolerable to the patient. During one year of therapy with ruxolitinib, leukocytes decreased only slightly from 7.5 to 5.0 GPt/l, while platelets remained stable at around 150 GPt/l. Monocytes dropped from 2.8 to 1.5 GPt/l (Figure 1).

Two follow-up BME after 2 and 15 months of treatment revealed a reduced blast percentage of 6 and 8.5% (Figure 1). The VAF of SRSF2 remained stable (at 3%) as well as the TET2-mutations (50% and 22%). The treatment was associated with strong symptomatic relief, namely the absence of night sweats and reduction of fatigue. The ultrasound control showed a normal-sized spleen after one year. Remarkably there were no side effects apart from anemia during the observation period. Importantly, no severe infections occurred in contrast to accumulating reports about immunosuppressive complications of ruxolitinib.[12]

Altogether, this case shows that ruxolitinib is well-tolerated and associated with symptomatic benefit in CMML-2. In contrast to the CMML-1 patients of the phase-1 study by Padron et al.,[5] the symptomatic improvement in our patient was accompanied by a reduction of blast percentage in the bone marrow.

Furthermore, CMML-2 is usually associated with a median survival of 13 months with less than 20% patients being alive 2 years after diagnosis.[13] Our patient has been on ruxolitinib for two years now and is still almost asymptomatic, which is remarkable given the progressive course and the poor prognosis of the disease. Of course, no definitive conclusions can be made from one patient treated, but our observation suggests a disease-modifying activity of ruxolitinib in CMML-2, that should be further investigated in clinical trials.

**Potential conflict of interest:** Disclosure forms provided by the authors are available with the full text of this article online at http://dx.doi.org/10.1080/10428194.2016.1225209.

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