Ruxolitinib as a bridge to allogeneic hematopoietic cell transplantation in a patient with idiopathic myelofibrosis

Uso de ruxolitinib como tratamiento puente al trasplante alogéncico de progenitores hematopoyéticos en un paciente con mielofibrosis idiopática

Dear Editor,

The recent development of Janus kinase (JAK) inhibitors has modified the treatment of primary and secondary myelofibrosis (MF). However, allogeneic haematopoietic progenitor cell transplantation (allo-HPCT) is still the only treatment option for these patients. This is a procedure restricted to young patients (<65 years of age) and those in good general condition, which are a minority of the patients affected by this disease. Moreover, typical aspects of patients with MF, such as splenomegaly and constitutional symptoms, have been associated with greater morbidity and mortality during the allo-HPCT procedure.\(^1\)

Treatment with ruxolitinib, a JAK-1 and JAK-2 inhibitor, has been demonstrated to reduce splenomegaly and improve the patients’ functional status by controlling the constitutional symptoms associated with MF in patients that are not candidates for transplantation. For that reason, it has recently been proposed for use before allo-HPCT in order to improve procedure results.\(^2\) However, experience of the use of this drug in this context is still limited.

We present the case of a male patient with MF who received treatment with ruxolitinib prior to allo-HPCT with the purpose of reducing splenomegaly and improving his functional status.

The patient was a 48-year-old male who had been diagnosed in December 2012 with post-essential thrombocythemia myelofibrosis, positive JAK-2, and an intermediate-2 international prognostic score. He presented pronounced asthenia, weight loss, a generally poor condition (Eastern Cooperative Oncology Group Score [ECOG] = 2), and splenomegaly of 18 cm as measured by ultrasound scan. Upon availability of an HLA-matched sibling, allo-HPCT with peripheral blood progenitor cells was indicated. In this context, and in order to reduce the splenomegaly and improve the patient’s ECOG score, a course of 20 mg/12 h of ruxolitinib was indicated during the 3 months prior to transplantation.

The treatment was tolerated well, and the patient gained weight (5 kg), improved his functional status (ECOG = 0) and the splenomegaly was reduced (10 cm). The only complication he presented was a slight decrease in platelet count that did not require dose adjustment. During the week before the beginning of the conditioning, the ruxolitinib dose was progressively reduced until suspension the day before chemotherapy was initiated. During the period of ruxolitinib dose reduction, the patient did not present any clinical or analytical alterations. The patient received reduced-intensity conditioning with fludarabine (150 mg/m\(^2\)), busulfan (6.4 mg/kg iv) and thiotepa (10 mg/kg). As prophylaxis for the graft-versus-host disease (GVHD), tacrolimus and rapamycin were administered. He presented haematopoietic recovery of neutrophils (>0.5 × 10\(^9\)/l) on day 22 and of platelets (>50 × 10\(^9\)/l) on day 28.

Two months after the allo-HPCT, the JAK-2 V617F mutation in peripheral blood was not detectable (Fig. 1). Currently, it has been 9 months since the allo-HPCT and the patient presents complete donor chimera, chronic GVHD grade I and no other complications.

This case shows that the use of ruxolitinib is feasible in patients with MF as a bridge treatment to allo-HPCT. Its use is justified by this drug’s capacity to reduce splenomegaly and improve the patient’s functional status, probably by controlling cytokine levels (such as IL-6 and TNF), with minimum general toxicity.\(^3\)

Splenomegaly is a poor prognosis factor in the context of allo-HPCT.\(^4\) Surgical splenectomy or splenic irradiation has been used before allo-HPCT, although its use is still controversial\(^4,5\) due to the associated complications. To the contrary, ruxolitinib has been demonstrated to reduce splenomegaly during the first months of treatment, without adding significant toxicity.\(^3\) Likewise, the functional status of the patient candidate for transplantation has also been identified as an adverse prognostic factor for allo-HPCT.\(^5\) In phase 3 studies, ruxolitinib has been seen to improve patients’ functional status and quality of life compared to patients treated with the best treatment available,\(^7\) so its use could equally favour transplantation recipients.

The administration of ruxolitinib for 3–6 months could reduce the morbidity associated with this procedure in MF patients. However, the effects of this strategy must be appraised in prospective studies. There is only one recently published study with these characteristics, which included 14 patients with MF candidates for HPCT, and only one with MF secondary to essential thrombocytemia, like the case of our patient. The study showed the feasibility of this strategy, although the effect of the drug on the development of chronic GVHD and its final impact on survival will have to be determined in subsequent studies.

In the case reported herein, the second in the medical literature with post-essential thrombocythemia myelofibrosis, the use of ruxolitinib prior to allo-HPCT was well tolerated, safe, and provided control over some of the factors associated with poor prognosis after these procedures.

References


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Selection criteria for search for germ mutations in colorectal cancer hereditary nonpolyposis

Criterios de selección para la búsqueda de mutaciones germinales en el cáncer colorrectal hereditario no polipósico

Dear Editor,

Members of families affected by hereditary nonpolyposis colorectal cancer (HNPPC), or Lynch Syndrome, may benefit from clinical examination programs. However, for these programs to be effective, they must be provided to those patients that are carriers of germline mutations in one of the mismatch repair (MMR) system genes. Therefore, when programmes that identify syndrome carriers do not preselect subjects to be studied, the low detection rates obtained make these programmes economically unfeasible. The application of the classic “Amsterdam criteria” as a selective pattern before genetic analysis is excessively strict since only 50% of mutation carriers comply with it. In addition, when the family history is not considered, the frequency of mutation detection is very variable (2–63%) and depends on the selection criteria applied, such as age at tumour diagnosis or the presence of microsatellite instability (MSI) in the tumour tissue.

Our objectives were to analyse patients with primary colorectal carcinomas (CRC) diagnosed before 51 years of age, and: (1) the utility of MSI phenotype as an indicator of germline mutations in hMLH1 and hMSH2; (2) the utility of family cancer history and tumour location as parameters to indicate the existence of germline mutations in the aforementioned MMR system genes; and (3) to establish the efficacy of the combination of MSI phenotype expression in tumour tissue and early age at diagnosis to detect such germline mutations.

We selected a total of 44 patients diagnosed with CRC before the age of 51. A tumour tissue sample was obtained from each; DNA was extracted from peripheral blood (germline) and from tumour tissue (tumour line). The presence of germline mutations in all exon sections of hMLH1 and hMSH2 genes was determined by means of the denaturing gradient gel electrophoresis (DGGE) technique. International guidelines for MSI evaluation in colorectal cancer have been used to determine the existence and the degree of instability in repetitive DNA sequences. These guidelines established a panel of 5 microsatellites to define the MSI phenotype.

Based on clinical and family history, the patients were classified as Bethesda 1, 2 or 3 (b1, b2 or b3), according to their compliance with Bethesda guidelines: (a) Criterion 1: individuals who met Amsterdam Criteria; (b) Criterion 2: individuals who had 2 synchronous and metachronous tumours associated with CRC; and (c) Criterion 3: individuals who had a first-degree relative with CRC diagnosed before the age of 45, or colorectal adenoma diagnosed before the age of 40.

Regarding MSI, 43% of the cases (n = 19) showed microsatellite instability (MSI) phenotype, and the other 57% (n = 25), had a stable phenotype. All tumours with any alteration in the germline in hMLH1 or hMSH2 genes showed MSI phenotype. In addition, there was an association between the expression of the MSI phenotype and the identification of germline mutations in the hMLH1 and hMSH2 genes (p = 0.004). The frequency of germline mutations in these genes was superior to 13% (6/44), whereas, in the samples that expressed MSI phenotype, the frequency was superior to 31% (6/19). The “sensitivity” of the MSI phenotype to detect germline mutations was 100% (6/6).

With regards to family history, 9 cases (20%) met at least one of the Bethesda guideline requirements. The 4 patients classified as b1 developed highly unstable tumours, and 3 of them showed germline mutations in hMLH1 or hMSH2 genes. Both b2 presented germline mutations in hMSH2 genes together with high MSL. Finally, from the 3 patients classified as b3, one showed high MSI and the other 2 were stable. Altogether, there was a correlation between family history (b1, b2 or b3) and the presence of mutation in hMLH1 or hMSH2 genes (p < 0.001). This correlation became more significant with requirements 1 and 2, since 5 out of 6 cases that met those requirements showed mutations in one of these genes.

Tumour location was similar in both stable and unstable tumours.

In humans, CRC are tumours that most frequently express instability in the microsatellite sequences; this phenotype is present in around 13% of these tumours. The frequency of this instability varies depending on age at diagnosis and is higher in young individuals. When studying the instability of microsatellite sequences in the tumour tissue of patients aged <30 with CRC, Farrington et al. observed an incidence of almost 50%.

The frequency of germline mutations found in hMLH1 or hMSH2 genes in CRC varies depending on the selection criteria of the samples to be analysed. Thus, there is an increase in the mutation detection rate when the expression of MSI phenotype is combined with young ages. Along this line, Farrington et al. showed that when young ages were combined with MSI phenotype, the rate rose to 63%, as opposed to a rate of just 28% when only age was considered. In our study, we observed that when age was considered as the only factor of selection to find germline mutations in hMLH1 or hMSH2 genes, the detection rate dropped to 13%, versus 31% when combined with the presence of MSI phenotype in tumour tissue.

As for the sensitivity of the MSI phenotype as a selection factor, most studies indicate that it is high and in our series it is...