Biol Blood Marrow Transplant 22 (2016) 432–440

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis with Prior Exposure to Janus Kinase 1/2 Inhibitors

Mohamed Shanavas [1], Uday Popat [2], Laura C. Michaelis [3], Veena Fauble [4], Donal McLornan [5], Rebecca Klisovic [6], John Mascarenhas [7], Roni Tamari [8], Murat O. Arcasoy [9], James Davies [10], Usama Gergis [11], Oluchi C. Ukaegbu [12], Rammurti T. Kamble [13], John M. Storring [14], Navneet S. Majhail [15], Rizwan Romee [16], Srdan Verstovsek [17], Antonio Pagliuca [5], Sumithira Vasu [6], Brenda Ernst [4], Eshetu G. Atenafu [18], Ahmad Hanif [3], Richard Champlin [2], Parameswaran Hari [3], Vikas Gupta [1,*]

[1] *MPN Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada*
[2] *Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, Texas*
[3] *Department of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Department of Hematology and Oncology, Mayo Clinic Cancer Center, Scottsdale, Arizona*
[5] *Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, United Kingdom*
[6] *Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus, Ohio*
[7] *Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York*
[8] *Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, New York*
[9] *Division of Cellular Therapy and Hematologic Malignancies, Duke Cancer Institute, Duke University School of Medicine, Durham, North Carolina*
[10] *Oxford University Hospitals NHS trust, Oxford, UK*
[11] *Department of Medicine, Weill Cornell Medical College, New York, New York*
[12] *Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*
[13] *Center for Cell and Gene Therapy, Baylor College of Medicine and Houston Methodist Hospital, Houston, Texas*
[14] *Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada*
[15] *Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio*
[16] *Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri*
[17] *Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms, Department of Leukemia, MD Anderson Cancer Center, Houston, TX, US*
[18] *Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Article history:
Received 10 September 2015
Accepted 6 October 2015

Key Words:
JAK1/2 inhibitors
Ruxolitinib
Myelofibrosis
Allogeneic transplantation
Survival

A B S T R A C T

The impact of Janus kinase (JAK) 1/2 inhibitor therapy before allogeneic hematopoietic cell transplantation (HCT) has not been studied in a large cohort in myelofibrosis (MF). In this retrospective multicenter study, we analyzed outcomes of patients who underwent HCT for MF with prior exposure to JAK1/2 inhibitors. One hundred consecutive patients from participating centers were analyzed, and based on clinical status and response to JAK1/2 inhibitors at the time of HCT, patients were stratified into 5 groups: (1) clinical improvement (n = 23), (2) stable disease (n = 31), (3) new cytopenia/increasing blasts/intolerance (n = 15), (4) progressive disease: splenomegaly (n = 18), and (5) progressive disease: leukemic transformation (LT) (n = 13). Overall survival (OS) at 2 years was 61% (95% confidence interval [CI], 49% to 71%). OS was 91% (95% CI, 69% to 98%) for those who experienced clinical improvement and 32% (95% CI, 8% to 59%) for those who developed LT on JAK1/2 inhibitors. In multivariable analysis, response to JAK1/2 inhibitors ($P = .03$), dynamic international prognostic scoring system score ($P = .003$), and donor type ($P = .006$) were independent predictors of survival. Among the 66 patients who remained on JAK1/2 inhibitors until stopped for HCT, 2 patients developed serious adverse events necessitating delay of HCT and another 8 patients had symptoms with lesser severity. Adverse events were more common in patients who started tapering or abruptly stopped their regular dose ≥6 days before conditioning therapy. We conclude that prior exposure

Financial disclosure: See Acknowledgments on page 439.

* Correspondence and reprint requests: Vikas Gupta, MD, FRCP, FRCPath, The Elizabeth and Tony Comper MPN Program, Princess Margaret Cancer Centre, Suite 5-303C, 610-University Avenue, Toronto, M5G 2M9, Canada.
E-mail address: vikas.gupta@uhn.ca (V. Gupta).

http://dx.doi.org/10.1016/j.bbmt.2015.10.005

to JAK1/2 inhibitors did not adversely affect post-transplantation outcomes. Our data suggest that JAK1/2 inhibitors should be continued near to the start of conditioning therapy. The favorable outcomes of patients who experienced clinical improvement with JAK1/2 inhibitor therapy before HCT were particularly encouraging, and need further prospective validation.

INTRODUCTION

Myelofibrosis (MF) is a group of neoplasms characterized by aberrant hematopoiesis, splenomegaly, inflammation-related symptoms, and an increased risk of leukemic transformation (LT) [1-3]. Dysregulation of Janus kinase (JAK)-signal transducer and activator of transcription pathway is the hallmark of MF, and JAK1/2 inhibitors have shown clinical benefit with reduction of splenomegaly and MF-related symptoms, regardless of *JAK2 V617 F* mutation status [4,5]. However, JAK1/2 inhibitors have limited activity on the neoplastic clones and do not reduce the risk of LT. At present, allogeneic hematopoietic cell transplantation (HCT) remains the only potentially curative therapy for MF [6-8].

High incidences of nonrelapse mortality (NRM) arising from graft failure, regimen-related toxicities (RRT), and graft versus host disease (GVHD) remain the major barriers to the success of HCT in MF [9-13]. Theoretically, JAK1/2 inhibitor therapy may help in overcoming some of these barriers [7,14,15]. Its potential benefits in this setting include (1) reduction in splenomegaly, which may facilitate engraftment; (2) decreasing symptoms due to proinflammatory cytokines; (3) improvement in performance status before HCT; and (4) a possible beneficial effect on GVHD [16]. However, conflicting data have emerged in the last 2 years on the safety of JAK1/2 inhibitors before HCT. Preliminary results of a prospective multicenter JAK-Allo Study from French researchers reported several serious adverse events, such as tumor lysis syndrome, cardiogenic shock, and sepsis, resulting in a temporary hold on recruitment [17]. On the contrary, small retrospective studies did not observe such events [18-22]. Additionally, there is a concern about potential risk of opportunistic infections due to the immunomodulatory effects of JAK inhibitors [23,24].

Another clinical dilemma faced by patients and treating physicians is the appropriate timing of HCT in a patient responding well to JAK1/2 inhibitor therapy: should one proceed with HCT while the patient is responding to JAK1/2 inhibitor therapy, or should HCT be reserved for the time of loss of response or intolerance to JAK1/2 inhibitors? At present, there is an equipoise in this area and no data to guide these decisions, and practice patterns vary. To understand some of the issues involved with the use of JAK1/2 inhibitors in the HCT setting, we conducted a retrospective multicenter study of MF patients who underwent HCT with a prior exposure to JAK1/2 inhibitors.

PATIENTS AND METHODS

Patients

This study was coordinated by the myeloproliferative neoplasm (MPN) program of the Princess Margaret Cancer Centre, Toronto. We contacted 20 centers with a major interest in MPNs and among these, 16 centers from Canada, United States, and United Kingdom participated in this study. Institutional research and ethics boards of respective centers approved this study. All centers reported data on consecutive patients who met eligibility criteria as below.

Adult patients who received first HCT for primary MF, MF secondary to polycythemia vera, or essential thrombocythemia and who had received treatment with either experimental or commercially available JAK1/2 inhibitors before HCT met the criteria for inclusion. Patients who had developed LT before starting JAK1/2 inhibitors were excluded. The primary endpoint was overall survival (OS). Secondary endpoints included the difference in OS between the groups based on response to JAK1/2 inhibitors and other transplantation outcomes.

Definitions

The dynamic international prognostic scoring system (DIPSS) before starting JAK1/2 inhibitor was used for disease specific risk stratification [25]. Comorbidities were scored using hematopoietic cell transplantation–specific comorbidity index [26]. Cytogenetics were delineated as normal, abnormal standard risk, and abnormal high risk, using an adaptation of the classification published by Caramazza et al. [27]. Conditioning intensity was classified as full-intensity conditioning or reduced-intensity conditioning according to the Center for International Blood and Marrow Transplant Research classification [28].

Patients who survived more than 14 days after HCT were evaluable for assessment of hematologic recovery. Dates of *platelet* and *neutrophil recovery* were defined as the first of 3 consecutive days of unsupported platelet count $\geq 20 \times 10^9$/L and absolute neutrophil count $\geq .5 \times 10^9$/L, respectively. *Primary graft failure* was defined as failure to recover absolute neutrophil count by day +35, as reported previously [6]. RRT was defined as per Bearman's criteria [29].

Classification of Responses to JAK1/2 Inhibitors before HCT

A working definition of response to JAK1/2 inhibitors was established inspired by revised response criteria by International Working Group-Myeloproliferative Neoplasms Research and Treatment [30] as follows: (1) group A, clinical improvement, defined as ≥50% improvement in palpable spleen length for spleen palpable by ≥10 cm, or complete resolution of splenomegaly for palpable spleen <10 cm; (2) group B, stable disease; (3) group C, increase in blasts to 10% to 19%, intolerance to treatment due to hematologic/non-hematologic side effects, or new onset transfusion-requiring anemia; (4) group D, disease progression manifesting as appearance of new splenomegaly palpable ≥5 cm below costal margin (BCM) or ≥100% increase in palpable distance BCM for baseline splenomegaly of 5 cm to 10 cm BCM, ≥50% increase in palpable distance BCM for baseline splenomegaly of ≥10 cm BCM, loss of spleen response, or symptomatic splenomegaly requiring splenectomy; and (5) group E, disease progression manifesting as LT, defined as a peripheral blood or bone marrow blast count of ≥20%.

Responses were assessed centrally based on the hematologic parameters and spleen sizes provided by the individual centers, and patients were stratified as above with the additional input from study investigators.

Definitions and Classification of Symptoms during Pretransplantation JAK1/2 Inhibitor Discontinuation

As the definitions of "rebound symptoms," "withdrawal symptom," or return of MF-related symptoms remain highly observer dependent [17,31-33], we reported all the potential new symptoms that occurred during pretransplantation discontinuation of JAK1/2 inhibitors and we explored their relationship with timing of drug discontinuation. Symptoms were graded, using clinical judgment, as mild, with symptoms not requiring any medical interventions; moderate, with symptoms requiring medical interventions including restarting of JAK1/2 inhibitors, unplanned use of steroids, oral analgesics for spleen pain (however, not requiring hospitalization or intravenous medications); severe, with symptoms requiring intravenous medications, hospital admissions, splenectomy, or delaying of HCT; or fatal, with death attributable to withdrawal symptoms.

Statistical Methods

Differences in continuous variables were tested using the Wilcoxon rank sum test and those of categorical variables were tested with chi-square or Fishers exact test, as appropriate. Patients who received a subsequent HCT were censored on the date of second HCT. Probabilities of OS were calculated by Kaplan-Meier method and differences between groups were estimated by log-rank test. Incidences of acute and chronic GVHD, neutrophil recovery,