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Rationale for combination therapy in myelofibrosis

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Agents targeting the JAK-STAT pathway have dominated the investigational therapeutic portfolio over the last five years resulting in the first and only approved agent for the treatment of patients with myelofibrosis (MF). However, chromatin modifying agents, anti-fibrosing agents, and other signaling pathway inhibitors have also demonstrated activity and offer the potential to improve upon the clinical success of JAK2 inhibition. Due to the complex pathobiological mechanisms underlying MF, it is likely that a combination of biologically active therapies will be required to target the MF hematopoietic stem cell in order to achieve significant disease course modification. Ruxolitinib in partnership with panobinostat, decitabine, and LDE225 are being evaluated in current combination therapy trials based on preclinical studies that provide strong scientific rationale. The rationale of combination of danazol or lenalidomide with ruxolitinib is mainly based on mitigation of anti-JAK2-mediated myelosuppression. Combination trials of ruxolitinib and novel anti-fibrosing agents such as PRM-151 represent an attempt to address therapeutic limitations of JAK2 inhibitors such as reversal of bone marrow fibrosis. Ruxolitinib is also being incorporated in novel treatment strategies in the setting of hematopoietic stem cell transplantation for MF. As the pathogenetic mechanisms are better understood, potential drug combinations in MF will increase dramatically and demonstration of biologic activity in effective preclinical models will be required to efficiently evaluate the most active combinations with least toxicity in future trials.

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This manuscript will address the proposed goals of combination therapy approach and review the state of the art in combination experimental therapy for MF.

Introduction

The approval of ruxolitinib (Jakafi, Incyte) by the Food and Drug Administration (FDA) in 2011 has greatly changed the treatment landscape of myelofibrosis (MF). Many intermediate and high risk MF patients with either enlarged spleens and/or the presence of MF-related symptoms are now being treated with ruxolitinib. Although the exact numbers of such patients are unavailable, it is presumed that many of the ruxolitinib-treated MF patients achieve a degree of improvement in symptom burden and reduction in spleen size that is deemed successful by the patient and/or treating physician. Keeping this in mind, the MF clinical investigator, now more than ever, is forced to critically re-evaluate treatment goals in a given MF patient. Broadly speaking, treatment goals can vary from purely palliative to curative, and can be specific such as amelioration of anemia, or attempt to modify the disease course. Patient and disease specific features influence the decision to focus on a particular treatment goal. Although ruxolitinib is effective for many MF patients in palliating symptoms and reducing splenomegaly, and recent analysis suggest prolongation of survival, it has not been shown to definitively alter the natural history of MF and this remains the focus of current clinical research. Due to the integral role of hyperactive JAK-STAT signaling in MF pathogenesis and the demonstrable clinical activity of JAK2 inhibitors, a number of clinical trials in 2014 are evaluating the safety and efficacy of JAK2 inhibitor combination therapy. This manuscript will highlight the challenge of determining which MF patients are appropriate for combination therapy and will review the state of the art of combination therapy for MF with emphasis on the preclinical rationale.

Patient case

The following case will serve as a basis for discussion regarding the appropriate role of combination therapy for MF and the different approaches that are currently being evaluated, including the rationale supporting each approach. A 60 year old male with treatment naive MF diagnosed three years ago presents with worsening anemia and the emergence of red blood cell transfusion dependence, night sweats, weight loss, and progressive splenomegaly over the last several months. He is stratified as high risk by the Dynamic International Prognostic Scoring System (DIPSS) and is initially prescribed ruxolitinib with rapid resolution of constitutional symptoms and moderate reduction of splenomegaly [1]. However, he continues to require frequent red blood cell transfusions with the continued documentation of peripheral blood blasts in the range of 3–5%. Although ruxolitinib has improved aspects of the disease process, transfusion dependent anemia and the potential for progression and/or transformation to acute leukemia remain a valid concern.

Therapeutic options for this individual include a) continued therapy with ruxolitinib until evidence of disease progression (enlarging spleen or increasing peripheral blood blast count), b) hematopoietic stem cell transplant (HSCT) if an appropriate donor is available, or c) experimental therapy. Experimental therapeutic options would include (but are not limited to) monotherapy with another JAK2 inhibitor (momelotinib, pacritinib, NS018, LY2784544, BMS911543), histone deacetylase inhibitor (panobinostat, pracinostat, givinostat, vorinostat), telomerase inhibitor (imetelstat), mTOR inhibitor (everolimus), hedgehog pathway inhibitor (LDE225, IPI-926), or antifibrosing agent (PRM-151, GS6624). Both the preclinical and clinical development of these agents as monotherapies are reviewed extensively elsewhere and are beyond the scope of this manuscript which will instead review combination therapy approaches under evaluation.