Case Report

Long-Term Use of Ruxolitinib in an AML Patient with Posttransplant Steroid Refractory GVHD

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Ruxolitinib has become a new therapeutic option for steroid refractory graft-versus-host disease (srGVHD), with a substantial remission rate. Its anti-inflammatory properties by blocking interleukin pathways have made it a novel therapeutic approach to inflammatory disease processes, such as GVHD. The long-term use of ruxolitinib has not been explicitly studied outside the context in the treatment of multiple myeloma. With current clinical trials underway for the use of ruxolitinib in srGVHD, there are still no current guidelines or protocols for long-term clinical use. Of the available literature showing ruxolitinib utilization for srGVHD, most cases lead to resolution and eventual discontinuation. We present a case of a 32-year-old male on ruxolitinib with GVHD status postmatched unrelated donor stem cell transplant (MUD SCT) for acute myeloid leukemia (AML) with FLT3 mutation currently on ruxolitinib for 5 years who is not able to tolerate reduction in dosage due to flare-ups. We discuss the clinical implications and nuance of therapy with ruxolitinib with unknown long-term effects and weigh the risks and benefits.

1. Introduction

Steroid refractory GVHD (srGVHD) has a poor prognosis, with survival rates between 5 and 30% [1]. Ruxolitinib has been shown to reduce side effects from srGVHD, in both acute and chronic settings, with some studies showing 81.5% overall response in an acute state and 46.3% in a chronic state [2]. Responses have been shown to occur mostly early in treatment with a 68% discontinuation rate and 21% reduction in steroid use [3]. Multiple centers have noted the promising effects [2, 3] along with clinical trials underway [4, 5].

Many of the best available treatments for srGVHD with current immunomodulatory drugs have side effects including lymphoproliferative disorders, relapse of disease, cancer, and opportunistic infections. While there have been reports of cytomegalovirus infection and pancytopenias on ruxolitinib [2, 6], others did not show these effects [3]. As dosages and treatments were similar, it is hard to speculate why there was a discrepancy between data sets. It is potentially due to the differing use of steroids and other immunosuppressive agents in conjunction with ruxolitinib. Further studies with sole administration of ruxolitinib are needed to determine if it is a causative agent for side effects or if there are other confounding variables.

To the authors’ knowledge, no studies have assessed the use of ruxolitinib in terms of long-term sequelae. Many effects have been noted in the treatment of sr-acute GVHD, but less for sr-chronic GVHD due to lack of necessity for further therapy with reduction of symptoms. Prolonged use of therapy due to inability to taper has not been specifically studied. This is due in part to the high percentage of patients who respond and ultimately are discontinued from therapy. Herein, we report our experience with a patient who responded to ruxolitinib and has been on the drug for 6 years with flare-ups despite prolonged taper schedule.

2. Presentation

A 26-year-old patient presented to an outside facility in late 2013 with a WBC count of 260,000, subsequently diagnosed with AML with FLT3 mutation, and started on emergent treatment. He was initially treated with 2 rounds of induction therapy with 7+3 regimen, but his disease state remained...
patient received azacytidine for 4 days at 75 mg/m² and was ease indicating hematological and morphological remission. marrow biopsy in February/2014 showed no activity of dis-
was discussed but ultimately decided to not be an option
rebiopsy in one month. At this time, a second transplant
continued on GM-CSF to help with GVHD with plans to
then started on sorafenib 200 mg BID and azacytidine and
biopsy 30 days from transplant showed minimal residual dis-
after transplant and received topical steroids. Bone marrow
methotrexate. The patient began displaying mild aGVHD
(4)/antithymocyte globulin regimen in November 2013.
he did receive a MUD SCT with fl
high-dose cytarabine 1500 mg/m² with sorafenib. Ultimately,
recombinant due to previous therapy, he was given a course of
fraction due to previous therapy, he was given a course of
immunosuppression at the time of his presentation consisted
methotrexate. The patient began displaying mild aGVHD
in steroid dose, and so MMF was discontinued and he
infections. Liver toxicity with longer-term use in patients
were seen as noted earlier. In our experience with this
have only identified one potential negative event
in terms of infection in an event of pneumonia. Even then,
could be due to multiple factors and not directly attribu-
ted to ruxolitinib, although this cannot be determined.
The authors of this paper speculate though that like any
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ted to ruxolitinib, although this cannot be determined.
The authors of this paper speculate though that like any
long-term immunosuppressive, clinical judgement should
be used to determine a risk/benefit analysis. In our specific
case, tapering causes severe GVHD flare-ups and hence the
reason for continued use. With no seemingly therapeutic
consequences of long-term use, we argue that there may be
no reason not to continue our patient on therapy and moni-
tor closely as with other immunosuppressive therapies.

Another consideration is the mechanism of action of rux-
olitinib versus other immunomodulating drugs. While both
are acting on regulation and proliferation of T-cells, ruxoli-
ribin acts on the Jak1/2 kinase pathways. The exact impact on
T-cell regulation and proliferation is still poorly understood
[7]. For example, in some studies, ruxolitinib decreased reg-
ulatory T-cells while in others, it increased [8]. There may
be more of an involvement in reduction of inflammatory
cytokines rather than absolute T-cell numbers compared to
calcineurin inhibitors.

There have been multiple studies highlighting the long-
term use of ruxolitinib in individuals with myelofibrosis with
side effects including pancytopenias, viral reactivation, and
infections. Liver toxicity with longer-term use in patients
with myelofibrotic disorders has been reported [9]. While
many studies were a different disease state, much of the
length of therapy overlaps with our patient to some extent.
It is reasonable then to state that the length of therapy in

3. Discussion

Given the relatively recent utilization of ruxolitinib for
srGVHD and the varying responses, the proper management
of patients on long-term therapy in the absence of clinical
guidelines is unclear. To date, no long-term toxicities have
been noted, although some infections and viral reactivations
have been seen as noted earlier. In our experience with this
patient, we have only identified one potential negative event
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length of therapy overlaps with our patient to some extent.
It is reasonable then to state that the length of therapy in
regard to our patient is in line with that in other uses for ruxolitinib in the context of long-term side effects. A final thought is that increased doses may harbor an unforeseen effect on the sr-cGVHD process. Most studies that have gone by the dosing parameters outlined by Zeiser et al. [2]. Our experience thus far has not shown any increased overall morbidity or mortality due to long-term ruxolitinib use. More studies and cases are needed to assess long-term outcomes of ruxolitinib use and if there are any side effects in the long-term, other than reported, to be weighed into management decisions.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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