The role of jak2 inhibitors in the management of cml: can we rest the case

Paolo Gallipoli

Cambridge Institute for Medical Research, University of Cambridge, UK

Correspondence: Paolo Gallipoli
E-mail: pg413@cam.ac.uk
Received: August 25, 2014
Published online: October 10, 2014

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder arising as a result of the reciprocal translocation between the long arms of chromosomes 9 and 22 (t9;22), leading to the formation of the fusion oncogene BCR-ABL. BCR-ABL has constitutive tyrosine kinase (TK) activity which is necessary for the transformed phenotype. The introduction at the end of the last century of BCR-ABL TK inhibitors (TKI) has dramatically changed the management of CML however despite their great efficacy, TKI are not curative. Disease persistence in CML patients treated with TKI lies in the insensitivity of the most primitive CML leukaemia stem cell (LSC). CML LSCs are not addicted to BCR-ABL kinase activity but rather rely on other stem cell intrinsic pathways for their survival. The main focus in the CML field is therefore to identify these pathways while also trying to exploit them therapeutically to achieve CML LSC eradication and as a result disease cure. Here we briefly review recent research on the role of the intracellular janus kinase (JAK) 2 in CML LSC survival and proliferation and discuss its putative role as a therapeutic target in CML. We discuss evidence supporting or dismissing a role for JAK2 in CML LSC survival and provide a possible explanation to reconcile the contrasting data published. We finally outline the future challenges which lie ahead of the CML community in trying to elucidate further the mechanisms of action of JAK2 and to translate into clinical practice the use of JAK2 inhibitors in CML.

To cite this article: Paolo Gallipoli. The role of jak2 inhibitors in the management of cml: can we rest the case. Sci Proc 2014; 1: e383. doi: 10.14800/sp.383.

Chronic myeloid leukaemia (CML) represents the most paradigmatic tumour in the field of cancer research. Since the original description of the Philadelphia chromosome (arising as a result of a reciprocal translocation between chromosomes 9 and 22) through the demonstration of the pathogenic role of the BCR-ABL oncogene to the clinical development of specific inhibitors of BCR-ABL kinase activity, CML has served as a paradigm of how a clear understanding of the molecular cause of a disease can lead to the rational development of specific targeted therapies with high therapeutic index and massive impact on disease outcome.

The management of CML, at least in its chronic phase, has been significantly impacted by the introduction of BCR-ABL tyrosine kinase inhibitors (TKI) with the vast majority of patients now achieving deep molecular responses, while enjoying good quality of life. However despite their remarkable efficacy TKI are unable to cure most of the patients. In fact even in patients achieving deep responses, including those with undetectable BCR-ABL transcript levels in peripheral blood, there is evidence of persistence of BCR-ABL+ cells at the stem cell level and of positivity for BCR-ABL genomic DNA by polymerase chain reaction (PCR). Furthermore, over 50% of patients achieving sustained undetectable BCR-ABL transcript levels show evidence of molecular relapse upon TKI discontinuation.
CML leukaemia stem cell (LSC) persistence is secondary to their insensitivity to TKI despite effective BCR-ABL kinase inhibition, suggesting that other pathways contribute to their survival \[12-13\]. Identifying such pathways and trying to exploit them therapeutically is paramount to achieve CML LSC eradication and disease cure.

Amongst such putative targets, the intracellular tyrosine kinase janus kinase (JAK) 2 has been the subject of investigations by several groups in an attempt to dissect its role in CML. JAK2 mediates cellular responses to several haemopoietic growth factors (GFs), primarily through phosphorylation and consequent activation of its downstream target, signal transducer and activator of transcription (STAT) 5. Over the last ten years, its role in haematological malignancies has come into focus, particular since the discovery of JAK2 activating mutations in BCR-ABL myeloproliferative disorders \[14-15\]. This latter discovery has led to the rapid development of numerous JAK2 pharmacological inhibitors, most of which have now reached clinical development \[16-17\] and are showing encouraging results. In CML however the role of JAK2 is less clear and current evidence has yielded conflicting results as to its role in BCR-ABL driven leukaemogenesis, thus creating confusion in regards to whether a therapeutic strategy targeting JAK2 should be pursued in CML.

While it appears that JAK2 might play a dispensable role in CML when BCR-ABL kinase is fully active \[18-19\], its role in the presence of an inhibited kinase or an attenuated kinase activity becomes more relevant \[20\]. However most JAK2 inhibitors used in preclinical studies have been shown to inhibit several other kinases alongside JAK2 thus casting doubts on the conclusions drawn, based on the use of these tool compounds, on the role of JAK2 in CML \[18, 21\].

We have recently addressed this issue by assessing the effects of the first clinically developed and specific JAK2 inhibitor, ruxolitinib, in the highly relevant model of primary human CD34+ CML cells in vitro and on leukaemia engraftment in vivo \[22\]. We show that combining ruxolitinib, at concentrations shown not to have any off-target effects on BCR-ABL itself, with the highly potent and specific TKI, nilotinib, results in a higher proportion of CML stem and progenitor cells, including the most primitive and quiescent ones, being eradicated compared to either treatment alone. The effects on the most primitive LSCs are further confirmed by the reduction of LSCs repopulating the bone marrow of NOD. Cg-Pkdcreoodles IL2rgm1WJflk1/Sizj mice (NSG) mice following combined treatment with ruxolitinib and nilotinib. These effects are, at least partially, secondary to a more profound inhibition of the JAK2 kinase activity as shown by the reduction in the phosphorylation levels of JAK2 and STAT5 and correlative changes on STAT5 target genes expression. These effects were only seen in the presence of GFs thus suggesting that JAK2 plays a prominent role only when activated by GFs in the presence of an inhibited BCR-ABL. These data can be reconciled with evidence by other groups confuting the role of JAK2\[18\] in CML when taking into account that 1) in those studies a different models was used (i.e. respectively BCR-ABL transduced murine bone marrow cells versus primary chronic phase CML cells, with the former likely expressing higher levels of BCR-ABL compared to the latter) 2) most of their in vitro work was performed in the absence of supplemented GFs and when BCR-ABL was still active (i.e. in the absence of TKI) and 3) that no secondary transplants were done so that any effect of JAK2 inhibitor on LSC exhaustion could not be assessed. We therefore believe that based on current evidence a therapeutic strategy targeting JAK2 in chronic phase CML patients warrants further study in clinical trials.

However several questions remain still to be answered in regards to the efficacy and safety of JAK2 inhibitors in CML patients:

1) Which other effects, beside its role in activating STAT5, does JAK2 have and do they play a role in the efficacy of ruxolitinib in vitro on CML LSC? JAK2 has already been shown to have other targets than STAT5: it can act as a histone kinase and chromatin modifier \[23\] while also being able to directly activate MYC \[24\] and β-catenin \[25\]. These and other yet unknown mechanisms could also be relevant and currently being investigated by ourselves and others in the CML community.

2) Can the role of JAK2 inhibitors be extended beyond CML chronic phase and in particular when inhibition of BCR-ABL kinase is not fully achieved? While it would appear logical to believe so, a degree of caution should be used as recent evidence has suggested that deletion of JAK2 might accelerate CML development in mouse models by preferentially causing elimination of normal haemopoietic stem cell compared to CML LSC where BCR-ABL is active, a situation often encountered in advanced phase disease carrying mutations in the kinase of BCR-ABL \[26\].

3) How safe is the use of JAK2 inhibitors in CML patients? While a therapeutic window has been shown by several studies using JAK2 inhibitors, a degree of toxicity towards normal bone marrow CD34+ cells has also been reported as a consistent feature \[20, 27\]. This is particularly relevant in chronic phase CML patients who often have a near normal quality of life on TKI, while enjoying good responses, and might influence clinicians and patients’ decision to use JAK2 inhibitors if this results in increased
toxicity, particularly bone marrow suppression. It is reassuring however that ruxolitinib has been used in patients with myelofibrosis without showing significant toxicity particularly in patients with adequate bone marrow function [16-17], the situation normally encountered in CML patients with minimal residual disease on TKI.

The ongoing work of the CML scientific and clinical community including the currently ongoing clinical trials of JAK2 inhibitors in CML patients (ClinicalTrials.gov identifiers: NCT01702064 and NCT01751425) will hopefully soon provide answers to all these questions.

In conclusion, the studies on JAK2 in CML highlight just one of the several potential survival mechanisms of CML LSC. Other putative targets have also been identified, particularly those interacting with p53 function such as the transcription factor B-cell lymphoma (BCL) 6 [28] and the deacetylase Sirtuin (SIRT) 1 [29]. The next step in the CML community is to try to identify more of such mechanisms and elucidate their interplay in order to devise even more effective, targeted and less toxic therapies against CML LSCs.

Acknowledgements

The author would like to thank Professor Tessa Holyoake for her support and supervision while performing the above mentioned research. This work was supported by the Glasgow Experimental Cancer Medicine Centre (ECMC), which is funded by Cancer Research UK and by the Chief Scientist's Office, Scotland. The author was funded at the time of undertaking research by a Medical Research Council UK clinical research training fellowship grant G1000288 and is currently funded by a National Institute for Health Research (NIHR) funding to cover his salary.

Authorship Contributions

P.G. designed and wrote the manuscript.

Conflict of interests

P.G. has previously received travel grants from Bristol-Myers Squibb.

References


