Ataluren-time for a 'no-nonsense' approach to haematological malignancies

John A. Loudon

Correspondence: jon.uk1515@gmail.com

Wetherill Park Medical Centre, Sydney, Australia.

Abstract

This article outlines the novel application of Ataluren - a readthrough agent - for the management of a number of haematological malignancies. A broad spectrum of cancers may be managed by this approach from solid-based to blood-borne. The focus here is on representing the spectrum of leukaemias that may be targeted by this novel therapy - as assessed via genetic screening for nonsense mutations in tumour suppressor genes. Reversion of such mutations can be hypothesized to be of significant value in the treatment of adult and childhood nonsense mediated-leukaemias. These are relatively prevalent and suited to the readthrough therapy approach.

Keywords: Acute lymphoid leukaemia, acute myeloid leukaemia, ataluren, chemotherapy, chronic lymphoid leukaemia, chronic myeloid leukaemia, haematologic malignancies, lymphoma, myeloma, myelodysplastic syndrome, nonsense mutation, readthrough, tumour suppressor

Correspondence

Haematological malignancy covers a group of cancers that affect blood, bone marrow and lymph nodes. Oftentimes all locations are affected simultaneously via their immune system interconnection. The cell of origin is both myeloid and lymphoid. Lymphomas, myeloma as well as lymphocytic leukaemias derive from lymphoid cells whereas myelogenous leukaemia, myelodysplastic and myeloproliferative conditions derive from the myeloid lineage.

Means of management of haematological malignancies include chemotherapy, radiotherapy, immunotherapy and, in selected cases, a bone marrow transplant. Treatment with *Glivec* targeting tyrosine kinase resulting from a specific genetic lesion in CML is proving to be a powerful therapy [1]. Another small molecular therapy is with Ataluren which specifically targets and reverts nonsense mutations - Premature Termination Codons - PTCs, by readthrough [2-4]. This low toxicity agent is being trialed for PTC-mediated cystic fibrosis and muscular dystrophy and can be also considered for use in PTC-mediated cancer and heart diseases [2-4]. Nonsense mutation reversion enables full length, potentially functional proteins, to be produced. The concept for cancer therapy is based on the observation that tumour suppressor genes exhibit a disproportionate number of nonsense mutational changes over oncogenes [4]. PTC mutations present in a whole variety of cancers from solid-based to haematological as can be gleaned from even a brief examination of COSMIC (Catalogue Of Somatic Mutations In Cancer, [4]).

Readthrough therapy of tumour suppressor PTCs in cancer has demonstrated 'proof of concept' for its benefits in cancer therapy in laboratory-based studies [2-4].

In terms of haematological malignancies the following highlight examples of tumour suppressors that may well be potentially excellent substrates for PTC-reversion and therefore could well prove highly efficacious in terms of a novel therapeutic approach. In AML a significant number of PTC-somatic mutations in the transcriptional corepressor gene *BCORL1* from various cell lines have been found [5]. In another instance in regards AML, the tumour suppressor, *PHF6*, is found to be mutated [6]. Genetic lesions in *PHF6* found in AML are both frameshift and nonsense mutations distributed through the gene. Another study [7] unveiled candidate tumour suppressor genes *FOXO3* and *PRDM1* in Natural Killer (NK)-cell neoplasms that were down-regulated in neoplastic samples. Nonsense mutations of *PRDM1* that led to functional inactivation in one cell line and one clinical sample were determined.

The classical tumor suppressor, *Tp53* has been examined in leukaemias and in CLL a significant number of PTCs in *Tp53* are found [8]. In ALL cell line *HPB* a novel PTC at codon 124 of *Tp53* has been disclosed adding weight to the direct involvement of PTC inactivation of this tumour suppressor in leukaemias [9]. In another study, the majority of *Tp53* mutations in myeloma patients were found to be PTCs [10]. Presence of *Tp53* mutations was associated with poor survival. Reversion of such *Tp53* PTCs in myeloma could therefore prove to be of considerable therapeutic value.

Mutation of cell cycle regulator p16 (*CDKN2A*) by PTC has been implicated in the genesis of paediatric T-cell acute lymphoblastic leukaemia [11]. Another cell cycle regulator, *CDKN1B*, has a tumor suppressor role and a PTC mutation found with tumour-tissue only in a case of acute lymphomatous adult T-cell leukaemia suggests a causative role [12]. A nonsense mutation in one

Table 1. Frequencies of somatic PTCs in selected key tumour suppressor genes as annotated on COSMIC for Haematopoietic and Lymphoid malignancies.

Gene	Number of unique PTCs
ATM	16
CDKN2A	4
MLH1	1
MSH2	1
PHF6	14
PRDM1	4
PTEN	14
Rb	2
RUNX1	14
Tet2	1902
Tp53	25

allele of *CDKN1B* in a case of T-cell prolymphocytic leukaemia implicates *CDKN1B* haploinsufficiency as a mechanism in the pathogenesis of this leukaemia [13]. PTC reversion of this allele can be predicted to be of therapeutic value in this case.

PTC mutation of *ATM* tumour suppressor has been linked to cancer formation [4]. Various somatic as well as germline *ATM* nonsense mutations have been implicated as causally related to mantle cell lymphoma – a non-Hodgkin's lymphoma [14]. Clearly, PTC reversion therapy could have a novel key role to play here.

A significant number of PTC mutations are potentially causatively related to *PTEN* tumour suppressor inactivation in radiation-induced thymic lymphomas in mice [15]. Again, this suggests investigating a place for reversion therapy targeting this suppressor gene in various human lymphoid neoplasms.

Tet2 is a tumor suppressor frequently mutated in haem-

atological malignancies [16]. Tet methylcytosine dioxygenase 2, whose function is not entirely understood, may have a significant role in epigenetic regulation. A study has shown that a majority of *tet2* mutations were of the nonsense type in patients with primary cytogenetically normal AML [17]. These patients had shorter event-free survival and therefore these mutations not only serve as useful prognostication markers but also as targets for PTC-based readthrough. *Tet2* nonsense mutations have been observed in chronic myelomonocytic leukemia, AML and myeloproliferative neoplasms and relate to poorer prognosis in AML [18]. Doubtlessly, any means to revert *tet2* PTCs would be highly valuable therapeutically in these instances.

Finally, a PTC in the *RUNX1/AML1* tumour suppressor gene, a known mutational target in AML, has been detected by whole transcriptome sequencing [19]. Again, this forms a useful target for Ataluren-based PTC-directed reversion therapeutics.

One caveat ought to be mentioned and that concerns drug resistance. As in most cancer therapies, resistance to chemotherapeutic agents occurs and Ataluren readthrough therapy may not be immune to that feature [2]. Time will tell to what degree this is of significance though in regards haematological malignancies yet clinicians should be aware of the potential for such an event.

Figure 1 summarizes a number of the above studies relating PTC and tumour suppressor genes in haematologic malignancies. Frequencies of somatic PTCs in selected key tumour suppressor genes in haematologic malignancies as annotated on COSMIC are listed in **Table 1**.

To conclude, PTCs are ubiquitous in leukaemias and inactivate a number of important malignancy-related tumour suppressor genes thereby decreasing vital intracellular levels of the protein product. In such a fashion, PTCs have a potentially causative role in haematologic malignancies. Reversion of these by low-toxicity small molecular agents such as Ataluren could be predicted to be of considerable value and a most useful addition to the therapeutic armamentarium of haemato- oncologists around the World. Thus the time is now right to commence clinical trials of Ataluren-based PTC readthrough therapy for haematological malignancies. Our future patients may well thank us for that!

Competing interests

The author declares no competing interests.

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