Novel molecular insights and targeted therapies in T-cell acute lymphoblastic leukaemia

S. Peirs, PhD

SUMMARY

Patients with T-cell acute lymphoblastic leukaemia are mainly treated with intensive combination chemotherapy. Although this treatment strategy is quite successful in children, refractory or relapsed disease is more difficult to treat. Moreover, the chemotherapeutic agents are associated with substantial toxicity. In order to find more effective and less toxic therapies, the genetic and epigenetic alterations in T-cell acute lymphoblastic leukaemia are studied and molecularly targeted drugs are being developed. In this thesis, two new strategies to treat T-cell acute lymphoblastic leukaemia were identified and evaluated. On the one hand, high expression of the anti-apoptotic factor *BCL2* was found as a hallmark of the immature T-cell acute lymphoblastic leukaemia subgroup. The BCL-2 specific inhibitor venetoclax proved to be a promising potential new therapy in T-cell acute lymphoblastic leukaemia and synergized with standard chemotherapeutic agents and BET bromodomain inhibitors. On the other hand, the enzyme KDM1A was identified as an interaction partner of the oncogenic transcription factor *ZEB2*. Antileukemic effects were demonstrated in several T-cell acute lymphoblastic leukaemia cell lines upon pharmacological inhibition of KDM1A.

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INTRODUCTION

T-cell acute lymphoblastic leukaemia (T-ALL) is a rare and aggressive blood cancer that originates from the malignant transformation of T-cell progenitor cells (lymphoblasts). Over the past decades, the cure rate for childhood T-ALL has gradually increased and is nowadays approaching 90%.[1] However, still a significant fraction of the children does not respond to therapy or relapses and presents with very dismal survival perspectives.[2] For adults, the survival rates are lower and the risk of relapse is higher.[3]

The current treatment of T-ALL patients consists of high-dose multi-agent chemotherapy, potentially followed by a hematopoietic stem cell transplantation. The chemotherapeutic agents often cause acute and long-term toxicities.[3,4] Therefore, more effective and less toxic therapies are needed for the treatment of T-ALL. By in-depth investigation of genetic and epigenetic alterations in T-ALL, a better understanding of the disease can be obtained. Unraveling the pathways and biological processes related to these alterations can lead to the identification of new druggable targets and eventually to the development of targeted therapies that are less toxic and more effective than the current ones.

In this PhD thesis, the aim was to find new treatment strategies for T-ALL by investigating the molecular mechanisms that contribute to the development of T-ALL. The main focus was on immature T-ALL, a subgroup of T-ALL characterized by a developmental arrest at the very early stages of T-cell development and a gene expression profile related to hematopoietic stem cells and myeloid progenitors.[5]

Center for Medical Genetics Ghent (CMGG), Ghent, Belgium.

Please send all correspondence to: S. Peirs, PhD, Center for Medical Genetics Ghent (CMGG), Medical Research Building 2, De Pintelaan 185, 9000 Ghent, Belgium, tel: +32 9 332 10 45, email: sofie.peirs@ugent.be.

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KEY MESSAGES FOR CLINICAL PRACTICE

1 The current treatment regimens using intensive multi-agent chemotherapy potentially followed by hematopoietic stem cell transplantation, cure about 90% of the children and 40% of adults with T-ALL.

2 There is still a need for more effective and less toxic drugs in the treatment of T-ALL.

3 By in-depth investigation of the molecular basis of T-ALL, new druggable targets can be identified and molecularly targeted therapies can be developed.

4 T-ALL can be added to the growing list of cancers that might benefit from treatment with the BCL-2 specific inhibitor venetoclax. Moreover, the preclinical data presented in this thesis provides a rationale to combine venetoclax with conventional chemotherapeutic agents or a BET bromodomain inhibitor.

THE ANTI-APOPTOTIC PROTEIN BCL-2 AS A PROMISING TARGET IN T-ALL

Although cancer cells experience various cytotoxic stresses, they can often resist apoptosis, a programmed form of cell death. One of the strategies that cancer cells can use to evade apoptosis, is increasing the expression of anti-apoptotic factors such as BCL-2.[6] The comparison of gene expression profiles between immature and other T-ALL patients, revealed a high expression of the *BCL2* gene as a hallmark of immature T-ALL.[7] This finding provided the rationale to evaluate BCL-2 inhibition as a novel therapeutic strategy for T-ALL. LOUCY, a human T-ALL cell line with a transcriptional program highly related to that of immature T-ALLs, exhibited high *in vitro* and *in vivo* sensitivity for the highly selective BCL-2 inhibitor venetoclax (synonym ABT-199, trade name Venclexta or Venclyxto, FDA approved for previously treated chronic lymphocytic leukaemia patients with 17p deletion) in correspondence with high levels of BCL-2.[11] In addition, especially primary T-ALL patient samples with a developmental arrest at the more early stages of T-cell development were sensitive to venetoclax treatment.[7]

In order to further increase the efficacy of venetoclax treatment and to lower the risk of developing resistance, combination strategies with venetoclax were investigated. In a first phase, we tested whether adding venetoclax to the current treatment schedule could be useful. Synergism between venetoclax and the chemotherapeutic agents doxorubicin, dexamethasone and L-asparaginase was found in human T-ALL cell lines.[7] Next, combinations with clinically relevant compounds were tested *in vitro* on a panel of patient-derived samples. This screen confirmed that venetoclax was able to enhance the antileukemic effects of several standard chemotherapeutics. However, the most promising combination was the one with the BET bromodomain inhibitor JQ1.[8] BET bromodomain inhibitors affect the expression of important (onco)genes and entered clinical trials for various cancers. Synergistic responses were also found in several human T-ALL cell lines in which the combination treatment induced strong cell death. Moreover, the treatment of cell line- and patient-derived xenograft mouse models with the combination of venetoclax and JQ1 outperformed the treatment with the single agents.[8]

KDM1A AS NOVEL INTERACTION PARTNER OF THE ONCOGENIC TRANSCRIPTION FACTOR ZEB2

ZEB2 is a transcription factor that is overexpressed in immature T-ALL patients compared to other T-ALL patients. Moreover, overexpression of *Zeb2* in a transgenic mouse model leads to the formation of immature T-ALL.[9] The development of small molecule drugs to directly target transcription factors is at present still very challenging. Therefore, we aimed to identify targetable protein interaction partners of the oncogenic driver *ZEB2* in the context of T-ALL via pull down experiments followed by mass spectrometry. One of the newly identified interaction partners was lysine-demethylase 1A (KDM1A, synonym LSD1). Cell lines derived from the *Zeb2* overexpressing transgenic mouse model were sensitive to *in vitro* treatment with the KDM1A inhibitor GSK2879552 (in clinical trials for acute myeloid leukaemia, myelodysplastic syndrome and small cell lung cancer). Interestingly, among the GSK2879552 sensitive lines in a human T-ALL cell line panel were cell lines with high *ZEB2* expression but also some with no or low *ZEB2* expression,

suggesting that other mechanisms or oncogenic drivers/transcriptional factors might be able to drive KDM1A inhibitor sensitivity. Surprisingly, the treatment of immunodeficient mice xenografted with GSK2879552-sensitive cell lines elicited only limited antileukemic responses. Hence, inhibition of KDM1A in human T-ALL might be particularly useful as part of a combination therapy.[10]

CONCLUSIONS

Two new strategies to treat T-ALL were identified and evaluated in *in vitro* and *in vivo* models. First, the BCL-2 specific inhibitor venetoclax proved to be a promising drug to treat T-ALLs that depend on the anti-apoptotic factor BCL-2 for their survival. Moreover, its efficacy was further improved in combination with standard chemotherapeutic agents or a BET bromodomain inhibitor. Secondly, KDM1A was found as an interaction partner of the oncogenic driver ZEB2. Inhibition of KDM1A might be a new strategy to treat these T-ALLs.

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