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REVIEW Article

Ibrutinib: a promising novel therapy for B-cell hematologic malignancies

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ABSTRACT

B cell malignancies are hematological disorders that originate from either precursors or mature B cells. Uncontrolled proliferation of B lymphocytes occurs in B cell acute lymphoblastic/chronic lymphocytic leukemia and in both non-Hodgkin and Hodgkin lymphomas. Non-Hodgkin lymphoma is one of the most frequent types of malignancy in the United States, in contrast to Hodgkin lymphoma, and 85% of non-Hodgkin lymphoma originates from the proliferation of B lymphocytes. It is well known that, among high toxicity induced by single or combined therapy, the resistance to treatment and frequent relapsed/refractory disease are also real challenges in the treatment of the complex B-cell non-Hodgkin lymphomas. Thus, new strategies for treatment are urgently needed. Ibrutinib (PCI-32765) is a new therapy for hematological malignancies, affecting the mature B-cell. Recently approved by FDA for the ttreatment of patients with mantle cell lymphoma and chronic lymphocytic leukemia and also designated by European Medicines Agency as an orphan drug for rare conditions, such as diffuse large B-cell lymphoma and follicular lymphoma, Ibrutinib could be a great strategy for the treatment of non-responders to the first-line therapies, with a tremendous potential for elderly patients. Due to the irreversible covalent binding of Ibrutinib with Bruton's tyrosine kinase (Btk), a great efficacy and less toxicity were reported for small lymphocytic lymphoma, prolymphocytic leukemia, multiple myeloma, hairy cell leukemia, Waldenstrom's macroglobulinemia and marginal zone lymphoma. New insights into Ibrutinib's mechanisms of action and resistance to therapy may contribute to the development of novel strategies for personalized therapy of B-cell malignancies and also to a better control of the severe adverse reaction.

Keywords: Ibrutinib, Bruton tyrosine kinase, FDA approved drugs, clinical trials, non-Hodgkin lymphoma

Abreviations: Non-Hodgkin lymphoma (NHL), Bruton tyrosine kinase (Btk), Interleukin-2-inducible kinase (Itk), Phosphatidyl-inositol trisphosphat (PIP3), Btk-associated molecule (BAM11), Protein kinase C (PKC), Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), Prolymphocytic Leukemia (PLL), Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Diffuse large B-Cell Lymphoma (DLBCL), Multiple Myeloma (MM), Precursor-B Acute Lymphoblastic Leukemia (B-ALL), Waldenstrom's Macroglobulinemia (WM), Marginal Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL)

Introduction

According to the World Organization of Health, B cell malignancies are hematological disorders that originate from either precursors or mature B cells. B

cell acute lymphoblastic leukemia/lymphoma is characterized by uncontrolled proliferation of immature B lymphocytes, while in B cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) mature B cells are implicated. Also, mantle cell lymphoma (MCL), follicular lymphoma (FL), hairy cell leukemia (HCL), prolymphocytic leukemia (PLL), diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma are forms of peripheral B cell malignancies, affecting mature B lymphocytes. These are non-Hodgkin lymphomas[1]. It seems that B cells are also involved in the nodular lymphocyte predominant form of Hodgkin lymphoma (NLPHL), which is a particular subcategory different from the classical Hodgkin lymphoma, in terms of immunophenotype characteristics[2]. Hodgkin lymphoma is rare compared to other cancers, representing 0.6% of all new cancer diagnoses in the US, and 1% of all new cases of neoplasms in the entire world[2,3]. NLPHL represents only 4-5% of all Hodgkin lymphoma, and a small percent of 3-5% may progress to a diffuse large B cell lymphoma[2].

In contrast, non-Hodgkin lymphoma (NHL) is one of the most common types of malignancy in the USA, after prostate cancer, breast cancer, pulmonary and digestive malignancies, skin melanoma and bladder cancer[4]. 85% of non-Hodgkin lymphoma originates from the proliferation of B lymphocytes and only 15% from T lymphocytes[5]. Surveillance, Epidemiology and End Results (SEER) Program of National Cancer Institute estimates that 70,800 new cases with non-Hodgkin lymphoma will be diagnosed in 2014, representing 4,3% of all new cancer diagnoses in the United States. The current treatment includes radiotherapy, rituximab, purine nucleoside analogs and alkylating agents for indolent forms and bone marrow or stem cell transplantation for aggressive, recurrent forms. Unfortunately, a concerning very high number of patients with non-Hodgkin lymphoma is estimated to die in 2014: 18,990. Also, data analysis from SEER Program shows that the highest percent of non-Hodgkin lymphoma deaths are among patients between 75-84 years old[4]. These data highlight the importance of new strategies for treatment, especially for recurrent forms of disease and for elderly patients. Thus, the "accelerated approval" for Ibrutinib by the U.S. Food and Drug Administration - FDA - for treatment of patients with mantle cell lymphoma (November 2013)[6] and for patients with chronic lymphocytic leukemia (February 2014), provides valuable new therapy for non-Hodgkin lymphomas affecting the mature B-cell[7]. Also, European Medicines Agency designated Ibrutinib as an orphan drug for rare conditions, such as diffuse large B-cell lymphoma (November 2013)[8] and follicular lymphoma (January 2014)[9] (see **Table 1**). Several clinical trials have shown less toxicity and a promising efficacy of the "first-in-class" inhibitor, due to the irreversibly covalent binding of Ibrutinib to the Bruton's tyrosine kinase (Btk)[10-12].

Table 1- Ibrutinib: a new therapy for non-Hodgkin and other B-cell lymphomas

Status	Indications	Dosage and Administration
FDA approved	Patients with *mantle cell lymphoma* who have received at least one prior therapy	Capsules, oral administration, 560 mg/daily
FDA approved	Patients with *chronic lymphocytic leukemia* who have received at least one prior therapy	Capsules, oral administration, 420 mg/daily
European Medicines Agency – designated as an orphan drug (EU/3/13/1203)	Patients with *diffuse large B-cell lymphoma*	-
European Medicines Agency – designated as an orphan drug (EU/3/13/1212)	Patients with *follicular lymphoma*	-

Targeting the Bruton tyrosine kinase

Ibrutinib (PCI-32765) inhibits the activation of the mature B-cell via selective and irreversible blocking of the Bruton tyrosine kinase (Btk) and its downstream pathways, important in B-cell receptor signaling[13]. Btk is one of the five members of Tec family kinases, along Tec, Itk, Bmx/Etk and Txk/Rlk[14]. Btk is important for B lymphocyte development, proliferation and differentiation[15]. Also, Btk is involved in adhesion and migration of B-cells, since the blocking of the tyrosine kinase with Ibrutinib inhibited adhesion and migration of primary CLL cells[16]. The structure of Btk consists of five domains: the N-terminal domain (PH), the Tec homology domain (TH) and the Src homology domains (SH3, SH2, SH1)[14] (see **Figure 1**). As reviewed by Hendriks et al., important protein interactions of Btk with various regulators of cell signaling are possible through these five domains, such as the N-terminal PH domain of Btk is responsible for binding of PIP3, BAM11, PKC and FAS, the SH3 domain is important for interaction with SAB (SH3B5), SYK and CBL and the C terminal domain is involved in interaction with FAS, PLCγ2 and caveolin 1[17]. Ibrutinib inhibits Btk through covalent and irreversible binding at C481 residue in the C-terminal domain[13]. Dasatinib, LFM-A13 and ONO-WG-307 are 3 other inhibitors of Btk, but all are characterized by reversible inhibition of Btk. Also, CC-292 seems to inhibit Btk through an irreversible covalent bond at C481, but only a few clinical trials in early phases are described so far[18]. Interestingly, a recent study also highlights the great potential of Ibrutinib in diseases affecting the T-cell, through an irreversible binding to the interleukin-2-inducible kinase (ITK)[19].

Challenges and future perspectives with Ibrutinib

FDA's "accelerated approval" of Ibrutinib for MCL and CLL patients, non-responders to other therapies, was based on a promising efficacy of Ibrutinib reported in two open-label, multi-centered trials, performed on 111 patients with MCL with an Overall Response Rate (ORR) of 65.8% (95% CI: 56.2%, 74,5%) with partial response in 48.6% and complete response in 17.1% and on 48 patients with CLL with an ORR of 58.3% (95% CI: 43.2%,

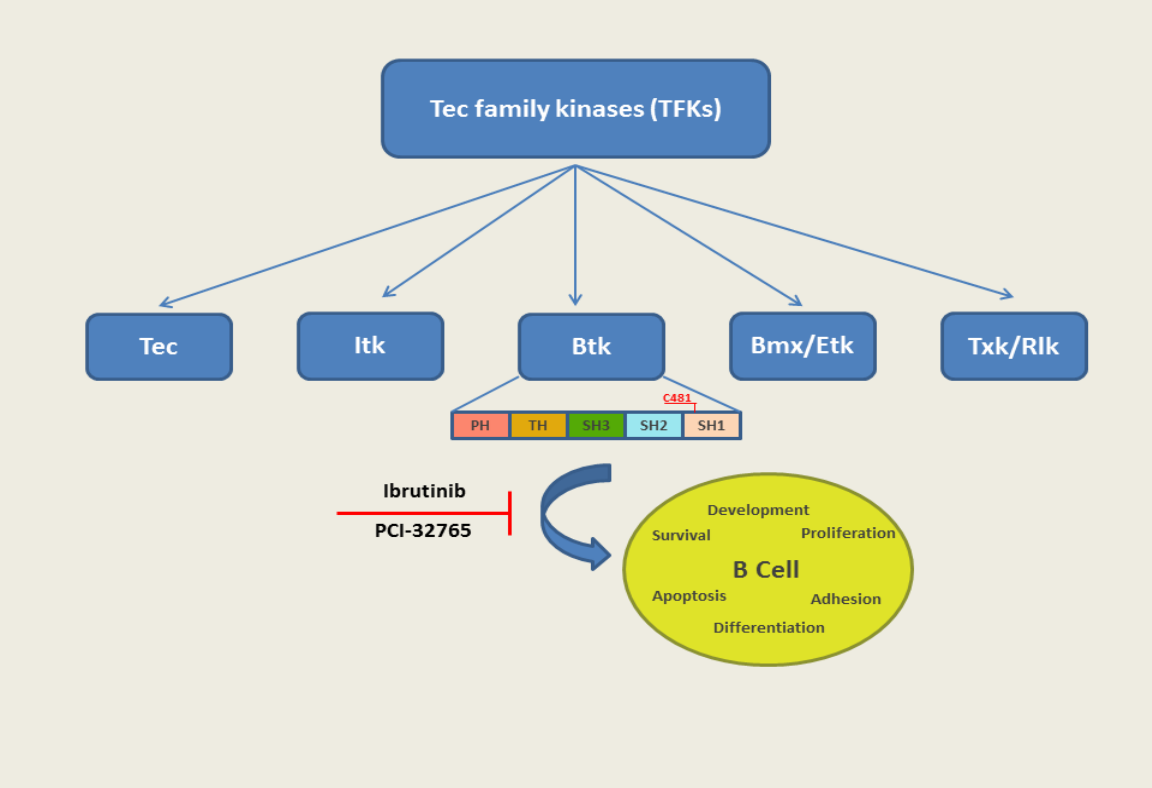

Figure 1 – Tec family kinases (TFK)s with focus on Bruton's tyrosine kinase (Btk) and Ibrutinib

72,4%), all partial responses and no complete response[20]. Ibrutinib has a simple treatment algorithm, including the oral administration of 3 capsules x 140 mg (420 mg/per day for chronic lymphocytic leukemia) or 4 capsules x 140 mg (560 mg/per day for mantle cell lymphoma)[20]. Although the encouraging efficacy of Ibrutinib in non-responders to other therapies and the easy treatment schedule could improve the compliance of the patient, it is very important to carefully monitor the possible severe adverse reactions[21]. A better understanding of mechanisms of action of Ibrutinib is absolutely necessary for a better control of the severe adverse reaction. It is well known that among high toxicity induced by single or combined therapy, the resistance to treatment and frequent relapsed/refractory disease are also real challenges in the treatment of the complex B-cell non-Hodgkin lymphomas[22]. One mechanism incriminated for the resistance to the Ibrutinib treatment seems to be a mutation in C481 residue of Btk, which is an important site for the covalent, irreversible binding of the inhibitor to the kinase[23,24]. Also, other mutations in downstream signaling of Btk, for example, in PLCγ2, could be involved[23]. The resistance to therapy remains a major concern, and further studies are needed to elucidate the mechanisms responsible for the reduced efficacy of Ibrutinib in some patients. Unfortunately, as reviewed by Stancu et al., Ibrutinib is one of the most expensive long-term treatments used in oncology, and this could also limit its use[25].

Up to date clinical trials: safety and efficacy studies

Currently, there are 60 clinical trials for Ibrutinib/ PCI-32765 registered in the database of U.S. National Institutes of Health (ClinicalTrials.gov)[26] (see **Table 2**). Thus, up to date, 46 early studies in Phase I and II proposed to investigate the safety and the efficacy of Ibrutinib alone or in combination with other drugs for a variety of hematological diseases: chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), prolymphocytic leukemia (PLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), diffuse large B-Cell lymphoma (DLBCL), multiple myeloma (MM), hairy cell leukemia (HCL) Waldenstrom's macroglobulinemia (WM) and marginal zone lymphoma (MZL)[26]. Ibrutinib could be a great strategy for treatment of non-responders to the first-line therapies, with a tremendous potential for elderly patients. For example, a recent clinical

Table 2 – Clinical Trials for Ibrutinib/ PCI-32765 registered in the database of the U.S.A. National Institutes of Health (www.ClinicalTrials.gov)

ClinicalTrials.gov Identifier	Type of study	Study design	Study Phase	Condition	Status
NCT01674322 NCT01866033 NCT01626651 NCT01969266 NCT01820936 NCT01763021	Interventional	Pharmacokinetics	I	Healthy volunteers	Completed
NCT01767948	Interventional	Pharmacokinetics	I	Liver diseases	Completed
NCT01292135	Interventional	Safety	I	CLL/SLL	Completed
NCT00849654	Interventional	Safety	I	Recurrent BCL	Completed
NCT02159755	Interventional	Safety	I	Recurrent MCL	Recruiting
NCT02109224	Interventional	Safety	I	Relapsed/ Refractory B-Cell NHL in patients with HIV infection	Not yet recruiting
NCT01569750	Interventional	Safety	I	CD20+ B-cell NHL	Ongoing
NCT01479842	Interventional	Safety	I	Relapsed DLBCL/MCL/Indolent NHL	Ongoing
NCT01955499	Interventional	Safety	I	Relapsed/ Refractory B-Cell NHL	Recruiting
NCT01886859 NCT02160015	Interventional	Safety	I	Relapsed/ Refractory CLL/SLL	Recruiting
NCT01829568	Interventional	Safety	I	Untreated FL	Recruiting
NCT01704963	Interventional	Safety/Efficacy	I	Recurrent Mature BCL	Ongoing

Table 2 – continued

ClinicalTrials.gov Identifier	Type of study	Study design	Study Phase	Condition	Status
NCT02055924	Interventional	Safety/Efficacy	I	BCL	Recruiting
NCT02077166	Interventional	Efficacy	I, II	Relapsed/ Refractory DLBCL	Recruiting
NCT01105247	Interventional	Safety	I, II	CLL/SLL	Completed
NCT02142049	Interventional	Safety/Efficacy	I, II	Relapsed/ Refractory DLBCL	Not yet recruiting
NCT01752426	Interventional	Safety/Efficacy	I, II	CLL, SLL	Ongoing
NCT01217749	Interventional	Safety/Efficacy	I, II	Relapsed/refractory CLL/SLL, PLL	Ongoing
NCT02013128	Interventional	Safety/Efficacy	I, II	CLL, MCL	Recruiting
NCT01962792	Interventional	Safety/Efficacy	I, II	Relapsed/ Refractory MM	Recruiting
NCT01500733	Interventional	Efficacy	II	CLL/SLL (patients ≥65 years old or with 17p Deletion)	Ongoing
NCT01744691	Interventional	Efficacy	II	Relapsed/ Refractory CLL/SLL with 17p Deletion	Ongoing
NCT01841723	Interventional	Efficacy	II	Relapsed HCL	Recruiting
NCT02129062	Interventional	Efficacy	II	Relapsed/ Refractory B-ALL	Recruiting
NCT01849263	Interventional	Efficacy	II	Relapsed/ Refractory FL	Recruiting
NCT01589302	Interventional	Efficacy	II	Relapsed/Refractory CLL/SLL/PLL	Recruiting
NCT01109069	Interventional	Safety	II	BCL CLL/SLL	Recruiting
NCT01236391	Interventional	Safety/Efficacy	II	Relapsed/refractory MCL	Completed
NCT02141282	Interventional	Safety/Efficacy	II	Relapsed/refractory CLL	Not yet recruiting
NCT01520519	Interventional	Safety/Efficacy	II	CLL/SLL	Ongoing
NCT01599949	Interventional	Safety/Efficacy	II	MCL	Ongoing
NCT01325701	Interventional	Safety/Efficacy	II	Newly Diagnosed/ Relapsed/Refractory DLBCL	Ongoing
NCT01614821	Interventional	Safety/Efficacy	II	WM	Ongoing
NCT01779791	Interventional	Safety/Efficacy	II	Refractory FL	Recruiting
NCT02007044	Interventional	Safety/Efficacy	II	Relapsed CLL	Recruiting
NCT01880567 NCT02169180	Interventional	Safety/Efficacy	II	Relapsed/ Refractory MCL	Recruiting
NCT01478581	Interventional	Safety/Efficacy	II	Relapsed/refractory MM	Recruiting
NCT01980628	Interventional	Safety/Efficacy	II	Relapsed/refractory MZL	Recruiting
NCT01980654	Interventional	Safety/Efficacy	II	Untreated FL	Recruiting
NCT02048813	Interventional	Efficacy	III	Untreated CLL (patients 18-70 years old)	Recruiting
NCT01886872	Interventional	Efficacy	III	Untreated patients (≥65 years old) CLL	Recruiting
NCT01722487	Interventional	Safety/Efficacy	III	CLL/SLL (patients ≥65 years old)	Ongoing
NCT01611090 NCT01578707	Interventional	Safety/Efficacy	III	Relapsed/ Refractory CLL/SLL	Ongoing
NCT01646021	Interventional	Safety/Efficacy	III	Relapsed/ Refractory MCL who have received at least one prior therapy	Ongoing
NCT01724346	Interventional	Safety/Efficacy	III	CLL/SLL (Patients ≥65 years old)	Recruiting
NCT01804686	Interventional	Safety/Efficacy	III	CLL/SLL/MCL/FL/DLBCL	Recruiting
NCT01855750	Interventional	Safety/Efficacy	III	DLBCL (Non-Germinal Center B-Cell Subtype)	Recruiting
NCT01776840	Interventional	Safety/Efficacy	III	MCL	Recruiting
NCT01974440	Interventional	Safety/Efficacy	III	Previously treated indolent NHL	Recruiting
NCT01973387	Interventional	Safety/Efficacy	III	Relapsed/ Refractory CLL/SLL	Recruiting
NCT02165397	Interventional	Safety/Efficacy	III	WM	Recruiting
NCT01833039	Interventional	Safety	IV	Relapsed/ Refractory MCL	Ongoing

trial in phase IB/II proposed to evaluate safety and efficiency in 31 patients with CLL/SLL with more than 65 years old that are not eligible for chemotherapy or immunotherapy due to high risk of severe infections. Remarkable, after a median follow-up of 22.1 months 71% of 31 patients responded to Ibrutinib treatment, showing a promising efficacy of the Bruton tyrosine kinase inhibitor in elderly patients with CLL/SLL. After treatment with Ibrutinib, predominantly mild and moderate adverse reactions were observed: 68% of patients developed diarrhea, 48% had nausea, 32% fatigue and 10% had infections. Also, the study reports a case of neutropenia and one of thrombocytopenia[11]. Also a high response (68%) was observed after a median follow-up of 15.3 months in 111 patients with relapsed/refractory MCL, also suggesting an efficient drug for patients with MCL that don't respond to other therapies. In this phase II study, the adverse reactions were predominantly mild and moderate: diarrhea (50%), nausea (31%), low appetite (21%), upper respiratory tract infection (23%), but also severe reactions appeared in a few patients: neutropenia (16%), thrombocytopenia (11%) and anemia (10%)[27]. Ibrutinib also showed efficacy in a phase II study performed on 63 patients with WM, with a response rate of 77% in the group of patients presenting the wild-type CXCR4 and 30% in the group with WHIM-like CXCR4 mutations[28]. Also, a phase II study performed on 64 patients with CLL reported lymphocytosis after treatment with one single dose of Ibrutinib. The absolute lymphocyte count increased in more than 40% of patients within 24 hours of starting treatment[29]. More advanced studies in phase III that are currently ongoing or recruiting participants planned to confirm the efficiency and safety of Ibrutinib alone or in combination compared with other drugs for CLL, SLL, MCL, FL, WM and DLBCL[26]. Only one ongoing clinical trial in phase IV is registered in the database of ClinicalTrials.gov, with the estimated date for finalization in April 2014. This study recruited patients with relapsed or refractory MCL after previous therapy in order to monitor the adverse reactions caused by Ibrutinib and to collect safety information about the drug[26].

Conclusions

The treatment of the complex B-cell non-Hodgkin lymphoma is certainly challenging due to high toxicity induced by single or combined therapy, resistance to treatment and frequent relapsed/refractory disease. Ibrutinib is a promising novel therapy for mature B-cell hematologic lymphomas. It was recently approved by FDA for treatment of patients with mantle cell lymphoma and chronic lymphocytic leukemia, but progresses were also made in several clinical trials for other hematologic malignancies, such as Waldenstrom's macroglobulinemia, multiple myeloma, follicular lymphoma and diffuse large B-cell lymphoma. Clinical trials have shown less toxicity and a promising efficacy of the "first-in-class" inhibitor, due to the irreversibly covalent binding of Ibrutinib with Bruton's tyrosine kinase (Btk). Ibrutinib could be a great strategy for treatment of non-responders to the first-line therapies, with a tremendous potential for elderly patients. A better understanding of mechanisms of action of Ibrutinib may contribute to the development of novel strategies for personalized therapy of B-cell malignancies and also to a better control of the severe adverse reaction. The resistance to therapy is also a major concern, and further studies are needed to elucidate the mechanisms responsible for the reduced efficacy of Ibrutinib in some patients.

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