Review Article

Phosphatidyl-inositol 3-kinase inhibitors in the treatment of T-cell lymphomas

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Abstract: A significant proportion of patients with T-cell lymphoma relapse after induction or are refractory to treatments. Therefore, there is an urgent need to develop new drugs with innovative mechanisms of action and limited toxicity profiles. Given that phosphatidyl-inositol 3-kinases (mainly δ and γ isoforms) play a pivotal role in regulating the malignant T-cell growth, proliferation and survival through the phosphorylation of their common effector Akt/PKB, their inhibition is supposed to allow the control of the disease in T-cell lymphoma patients who relapse or show refractoriness to conventional treatment or to other labeled drugs. Duvelisib, copanlisib and RP6530 have shown promising results in this context, and their role is reviewed.

Keywords: Copanlisib; duvelisib; phosphatidyl-inositol 3-kinase; RP6530; T-cell lymphoma

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Introduction

A substantial proportion of patients with T-cell lymphoma, regardless their predominantly nodal or extranodal presentation, display progressive disease either during induction treatment or immediately before autologous transplantation, when this procedure is considered an option, or even relapse shortly after having obtained a clinical response after first-line treatment. For this reason, it is of uttermost importance to develop new treatment strategies in this peculiar category of diseases: on the one hand, in order to try to overcome chemoresistance and allow patients to achieve better survival rates and have access to transplantation procedures, while on the other to reduce off-target toxicities (1,2).

Purpose of this work is to review the current knowledge in terms of phosphatidyl-inositol 3-kinase (PI3K) inhibition in T-cell lymphoma, with a specific focus on innovative drugs now being tested in clinical trials (*Table 1*).

Phosphatidyl-inositol 3-kinase inhibitors: mechanism of action and biologic rationale

PI3K are a family of heterodimeric lipid kinases that integrate signals from different cell surface receptors, such as B-cell receptor, integrins, chemokine and growth-factors receptors, and in this way regulate most of the cell pathways involved in proliferation, metabolism, protein synthesis and survival. They are responsible of catalyzing the phosphorylation of the hydroxyl group on position 3 of the inositol ring of phosphatidylinositol 4,5-bis-phosphate (PIP2), which is then converted to phosphatidylinositol 3,4,5-triphosphate (PIP3), which in turns acts as a lipid second messenger (6).

These enzymes are made of a catalytic subunit (p110), which is responsible of the phosphorylating reaction. Different isoforms of the p110 subunit can be found in class IA PI3K: α and β isoforms are ubiquitously expressed and mainly regulate insulin signalling, angiogenesis and

Table 1 Experiences with PI3K inhibitors T-cell lymphoma patients

Treatment	Subunit inhibition (formula and molecular weight)	Patient number	Subtypes (patients)	ORR (%)	CR (%)	Median OS (months)	Median PFS (months)	Ref.
Duvelisib	p110 δ + p110 γ [$C_{22}H_{17}ClN_6O$ (416.86 g/mol)]	33	All patients	42	6	–	–	(3)
			All PTCL patients (PTCL-NOS =6; AITL =3; PLTCL =3; ALCL =2; EATL =1; NK/TCL =1)	53	13	8.4	8.3	
			All CTCL patients (MF =7; tMF =4; SS =5; cALCL =1)	33	0	NR	4.5	
Copanlisib	p110 α + p110 δ [$C_{23}H_{28}N_8O_4$ (480.53 g/mol)]	17	All patients (PTCL-NOS =10; AITL =4; ALCL =3)	21	14	NA	NA	(4)
RP6530	p110 δ + p110 γ [$C_{23}H_{18}FN_5O_2$ (415.43 g/mol)]	37*	All patients	45	10	NA	NA	(5)
			All PTCL patients	57	29			
			All CTCL patients	38	0			

*, 20 patients evaluable for response. ORR, overall response rate; CR, complete response; OS, overall survival; PFS, progression-free survival; NA, not assessed; NR, not reached; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma, PLTCL, panniculitis-like T-cell lymphoma; ALCL, anaplastic large cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; NK/TCL, NK/T-cell lymphoma; MF, mycosis fungoides; tMF, transformed mycosis fungoides; SS, Sézary syndrome; cALCL, cutaneous anaplastic large cell lymphoma.

platelet functions; the γ isoform is instead restricted to haematopoietic tissue. Class IB PI3K consists of the δ isoform (PI3Kδ), again preferentially expressed in human leukocytes, which plays a significant role in B-cell development and function, and whose signalling pathway seems particularly hyperactive in B-cell malignancies. Any catalytic subunit is associated to a regulatory subunit (p85α, p55α and p50α are associated with p110α; p85β with p110β; p55γ with p110δ; p101 and p84 with p110γ), which binds and stabilizes the catalytic subunit itself and inhibits its function. In presence of an activating signal, regulatory subunits relieve their inhibitory action, thus permitting phosphorylation (7).

Once PIP2 is converted into PIP3, several intracellular regulatory molecules are recruited closely to the plasma membrane and activated by phosphorylation: among those, Akt (also known as protein kinase B, PKB) is the most relevantly involved, as it plays a role in inducing the nuclear translocation of nuclear factor κB (NF-κB) transcription factors (which control cellular proliferation) and in stimulating the mammalian target of rapamycin (mTOR)-mediated protein synthesis and cell growth. Conversely, Akt/PKB itself inhibits the Forkhead box O (FOXO) family of transcription factors, with consequent cell cycle progression and inhibition of apoptosis, as well as the proapoptotic protein Bad (6-8).

The cell functions regulated by PIP3 are indeed strictly dependent on the cell context in which it operates and on the isoform of the p110 catalytic subunit engaged. Blockade of PI3K by means of orally or intravenously administered small molecules is nowadays possible, as many drugs are available (9): idelalisib, a selective and orally available PI3Kδ inhibitor, is the first Food and Drug Administration approved drug of this class, now with indications in relapsed/refractory chronic lymphocytic leukemia (administered together with rituximab) and follicular lymphoma (as a single agent) (10,11). Duvelisib and RP6530 (both PI3Kδ + PI3Kγ inhibitors) have also been tested in clinical trials (3,12,13), mainly involving indolent B-cell neoplasms, but also in some subsets of patients with T-cell lymphoproliferative disorders. Copanlisib, a pan-PI3K inhibitor, with enhanced activity on PI3Kα and PI3Kδ, is another agent widely tested in clinical trials (14,15). More PI3K inhibitors of the p110δ subunit (umbralisib, acalisib, INCB050465, ACP-319), or inhibitors of combined p110α + δ (pictilisib) and p110β + δ (KA-2237) are now being explored in clinical trials.

PI3K inhibition results in a series of scenarios: (I)

blockade of prosurvival signals mediated by the tonic signalling from the B-cell receptor (this is the main mechanism of action in B-cell lymphomas and chronic lymphocytic leukemia, mainly dependent on p110δ inhibition); (II) inhibition of cytokine signalling from the microenvironment through chemokine-mediated and adhesion molecules-mediated prosurvival signals, with a mechanism that again mostly relies on p110δ; (III) functional impairment of $CD8^+$ T-lymphocytes and reduction in the ability of $CD4^+$ T-lymphocytes to proliferate, expand and differentiate into helper T-cell subsets, as a consequence of p110δ inhibition, on which converge signals from the T-cell receptor; (IV) reduced chemotaxis of activated $CD4^+$ and $CD8^+$ T-cells via the stimulation of chemokine receptors, as a result of p110γ blockade; (V) decreased T-regulatory lymphocytes (T_{reg}) functions, which consequently counterbalance the impaired T-$CD4^+$ and $CD8^+$ function; (VI) possible enhancement of direct antitumor activity (6,8). The same mechanisms and signal transduction topography may explain the specific toxicities observed with these agents (8). Increased incidence of bacterial and opportunistic infections has been observed in patients receiving p110δ inhibitors, as well as an increased susceptibility to inflammatory processes of presumed autoimmune origin, like colitis, pneumonitis and hepatitis, as a consequence of decreased T_{reg} regulatory activity and enhanced $CD8^+$ T-cell-mediated cytotoxic activity (16). Pan-PI3K (more precisely, non-γ-non-δ) inhibition is more likely related to metabolic and vascular effects, like transitory hyperglycemia and hypertension (4,14,15).

Duvelisib

Formerly known as IPI-145, duvelisib is an orally administered small PI3K inhibitor, with full coverage of both δ and γ isoforms when administered at the dose of 25 mg, twice a day, or higher. The phase 1 study IPI-145-02 (NCT01476657) allowed enrolment of patients with advanced hematologic malignancies, with disease-specific expansion cohorts at the maximum tolerated dose (MTD), one of these specifically focusing on patients with pretreated peripheral T-cell lymphomas (PTCL) and cutaneous T-cell lymphomas (CTCL). The study was aimed at evaluating the safety and the pharmacokinetic profile of single-agent duvelisib, as well as assessing the MTD (3). Treatment was given twice a day (b.i.d.), continuously in 28-day cycles, at escalating doses ranging from 25 to 100 mg (doses of 25 mg and 50 mg b.i.d. were given to one patient each, while four patients received a dose of 60 mg b.i.d., 25 patients a dose of 75 mg b.i.d., and two patients a dose of 100 mg b.i.d.). The established MTD was 75 mg b.i.d.

Thirty-three patients with T-cell lymphomas were treated in the study. Seventeen patients were affected by CTCL: 11 patients had mycosis fungoides (4 of which showing transformation into a large-cell lymphoma), 5 had Sézary syndrome and 1 was affected by primary cutaneous anaplastic large-cell lymphoma. Sixteen patients had a PTCL: angioimmunoblastic T-cell lymphoma and panniculitis-like T-cell lymphoma were diagnosed in three patients each; six patients had a PTCL, not otherwise specified and two patients systemic anaplastic large-cell lymphoma; enteropathy-associated T-cell lymphoma and NK/T-cell lymphoma were diagnosed in one patient each. Median age at enrolment was 70 (range, 34–86) years for the PTCL group and 64 (range, 48–81) years for the CTCL group. Median number of systemic treatments was 4 (range, 1–11) for the entire cohort of patients, 2.5 (range, 1–7) and 6 (range, 2–11) for patients in the PTCL and CTCL cohorts, respectively. Median time interval elapsed from last therapy to first duvelisib dose was 1.05 (range, 0.2–36) months.

The majority of patients discontinued treatment because of disease progression (44% in the PTCL group and 53% in the CTCL group), whereas an adverse event was the cause of treatment discontinuation in 38% and 37% of the cases, respectively. The overall response rate (ORR) for the entire T-cell lymphoma population was 42%, including a complete response (CR) in 6% of cases. A stable disease was obtained in 21% of cases, whereas 36% of patients progressed. More specifically, among PTCL patients, the ORR was 53%, with 13% CR and 40% partial response (PR), and a median time to response of 1.9 (range, 1.5–3.5) months. CTCL patients achieved an ORR of 33%, with no CR documented, and a disease stability in a third of the cases. Median time to response in this subset of patients was 2.4 months, ranging from 1.6 to 3.8 months. Clinical activity was observed across all T-cell lymphoma subtypes, with CR seen in one patient with PTCL, not otherwise specified, and in one patient affected by enteropathy-associated T-cell lymphoma. The median progression-free survival (PFS) and overall survival (OS) for PTCL patients were 8.3 and 8.4 months, respectively, at a median time on study of 8.3 months; median PFS for CTCL patients was 4.5 months, whereas the median OS was not reached, at a median time on study of 14.7 months.

Pharmacodynamic results showed that a down-modulation of serum cytokines and chemokines related to T-cell activation and migration and to the microenvironment (such as CCL22, CXCL13, tumor necrosis factor-α, matrix metallopeptidase-9 and interleukin-16) occurred within 8 days of starting treatment. Pharmacodynamic response, as assessed by positron emission tomography (PET) scan at cycle 1, day 22, was predictive of clinical response: among the ten patients evaluated by PET at this time point, 6 showed a standardized uptake value (SUV) reduction, being able to achieve a subsequent clinical response (CR or PR) in 83% of cases (5 patients out of 6). On the contrary, all the four patients who showed an increased SUV at the first PET scan evaluation had disease progression while on treatment.

Adverse events (at least of grade 3) were observed in 79% of patients, with elevation of liver transaminases (36% of cases), cutaneous rash (21%) and neutropenia (15%) being the most common toxicities. The elevation of liver transaminases was the cause of treatment discontinuation in 14% of patients. Severe adverse events were reported in 51% of patients: pneumonia (23%), diarrhea (9%) and pyrexia (9%) were the most frequent. Colitis was observed in 6% of patients. Three patients died while on treatment, less than 30 days from their last dose: one because of disease progression, one as declined supportive therapy and one as a consequence of herpes virus-related pneumonia.

Based on these data, a phase 1 trial of duvelisib in combination with either romidepsin or bortezomib in relapsed or refractory T-cell malignancies has been designed and is now actively recruiting (NCT02783625).

Copanlisib

Copanlisib (BAY-80-6946) is a PI3K inhibitor administered intravenously with a predominant activity on α and δ isoforms. It has been approved by the Food and Drug Administration for the treatment of patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.

The results of a phase 2 study in 84 patients with relapsed or refractory indolent or aggressive lymphoma after at least two previous treatment lines have been recently published (CHRONOS-1 study, NCT01660451-part A) (14). The aggressive lymphoma cohort also included 17 T-cell lymphoma patients, and more specifically ten patients with PTCL, not otherwise specified, 4 with angioimmunoblastic T-cell lymphoma and 3 with systemic anaplastic large-cell lymphoma. Patients were treated with copanlisib at the dose of 0.8 mg/kg, which was given over a 1-hour infusion on days 1, 8 and 15 of a 28-day cycle. Treatment was allowed until disease progression or unacceptable toxicity.

Among the PTCL patients, 14 were eligible for response assessment: 2 (14.3%) patients obtained a CR and 1 (7.1%) patient a PR, yielding an ORR of 21.4% (given that the ORR for the whole aggressive cohort was 29.4%).

Hyperglycemia and hypertension were the most common treatment-emergent adverse events experienced by both cohorts of patients in the trial (59.5% and 54.8% of incidence, respectively), being consistent with the target profile of the drugs and its route of administration, as described in an earlier phase 1 trial (4). Both adverse events were transient and manageable and never higher than grade 3. Peaks of blood pressure and plasma glucose occurred at 1–2 hours and 5–8 hours after the start of infusion, respectively, followed by their decline to normal basal values. None of the patients in the trial discontinued their treatment because of either event. Opportunistic infections and pneumonitis were rather infrequent in the trial (2.4% and 3.6%, respectively), and aspartic-transaminase (AST) and alanine-transaminase (ALT) elevation was an incidental finding in 25.6% of patients (grade 1–2 in almost all cases). No cases of colitis have been reported, although diarrhea occurred in 35.7% (grade 1–2) and 4.8% (grade 3) of patients. Serious drug-related adverse events were recorded in 32.1% of patients.

RP6530 (tenalisib)

It is a novel and highly specific dual PI3Kδ and γ inhibitor, being able to inhibit Akt/PKB phosphorylation at nanomolar concentrations, which has demonstrated ability to induce apoptosis in lymphoma and leukemia cell lines. Chemically, it is a isoflavone-substituted adenine.

The interim results of a phase 1 study of RP6530 in patients affected by relapsed or refractory mature T-cell neoplasms, including PTCL and CTCL, were firstly reported at the 2016 American Society of Hematology (ASH) meeting (RP6530-1401 study, NCT02567656) and recently updated at the 2017 ASH meeting (5). The study is aimed at evaluating the safety, the pharmacokinetics and the MTD of RP6530 given orally, twice a day, in cycles of 28 days, through dose escalations from 200 to 800 mg b.i.d. It consists of a dose escalation phase and an expansion phase for both PTCL and CTCL patients. Based on dose limiting toxicities (see below), the MTD was determined to be 800

mg b.i.d fasting.

Data on 37 patients (17 PTCL and 20 CTCL) have already been disclosed (doses escalating from 200 to 800 mg b.i.d. + patients in the expansion cohort); 20 of these patients are evaluable for efficacy (as they have received at least 2 cycles of treatment) (5,13). Median number of prior therapies was 3 (range, 1–7) and 5 (range, 1–15) for PTCL and CTCL patients, respectively.

Most of the adverse events were grade 1–2. Grade 3 adverse events were observed in 13 out of the 37 enrolled patients, and included: AST and ALT elevation (24% of cases), rash (8%) and neutropenia (3%). Events were reversible and easily manageable in most of instances, without any treatment-related severe adverse events. Two patients discontinued treatment due to safety reasons. No drug-related colitis, pneumonitis or pneumonia have been reported so far.

Among the 20 patients evaluable for efficacy, 9 (45%) have obtained an objective response, with 2 (10%) CR and 7 (35%) PR. Stable disease was observed in 8 (40%) patients. More specifically, the ORR was 57% (with the 2 observed CR) in PTCL patients and 38% (with no CR and with 5 PR) in CTCL, respectively. Twelve patients experienced rapid disease progression while receiving initial cycles and discontinued treatment prematurely. Response was assessed by PET scan and computed tomography scan in patients with PTCL, and by modified severity-weighted assessment tool (mSWAT) in those with cutaneous disease.

Conclusions

Albeit results are still preliminary, PI3K inhibitors seem to play a relevant role in the treatment of T-cell lymphoma patients with relapsed or refractory disease, with significant ORR and limited toxicity, sometimes lacking class-specific immune-mediated toxic effects on liver, intestine and lungs. More efforts are required in order to find the best dosages, treatment durations and the most suitable collocation in the treatment algorithm of T-cell lymphoma patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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