Non-ATP competitive inhibition of PI3Kδ with IOA-244 shows anti-lymphoma activity

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Activation of PI3K signaling, mainly mediated via PI3Kδ, is a fundamental signaling cascade in lymphomas (Tarantelli et al, 2021). IOA-244 (IOA) is a highly selective and potent PI3Kδ inhibitor with atypical non-ATP competitive activity (John-son et al, 2019) compared to FDA-approved PI3K inhibitors idelalisib, copanlisib and duvelisib. IOA is in phase 1 as an immunomodulatory agent for patients with melanoma, mese-thothelioma, non-small cell lung cancer, myelofibrosis, and follicular and peripheral T cell lymphoma (TCL) as a single agent or in combination (NCT04328844). IOA doses up to 80 mg were well tolerated in the first 16 patients (Di Giacomo et al, 2021) and in follicular lymphoma patients (Carlo-Stella et al, 2021) and in follicular lymphoma patients (Di Giacomo et al, 2021) and in follicular lymphoma patients (Di Giacomo et al, 2021) and in follicular lymphoma patients (Di Giacomo et al, 2021). Here, we present the first set of data on IOA in our in vitro lymphoma studies in lymphoma.

BACKGROUND

MATERIAL AND METHODS

Cell lines were exposed to increasing concentrations of IOA and anti-proliferative activity was assessed by MTT assay at 72h. Apoptosis and cell cycle were assessed by FACS. Poly-A production by Annexin V/PI staining followed by FACS acquisition were assesses after treatment of lymphoma cell lines. The up-regulated (n=188) included proapoptotic factors (HRK, BIK), tumor suppressors (GADD45A, TP63, LGALS3, PDCD1), cytokines (CCL22, CXCL10, CCL2, CXCL12, CXCR5), angiogenic factors (VGEFA, VEGFC, VEGFD), immune checkpoint inhibitors (CTLA4, PD-1) and anti-lymphoma genes (BACH2), and immune-related factors (CXC4R, CTLA4).

RESULTS

IOA showed moderate dose-dependent anti-proliferative activity across 74 cell lines derived from B (n=59) and TCL (n=15) with IC50s < 1µM in only a few cell lines. B cell lyphomas, particularly mantle cell lymphoma (MCL) models (median AUC=666k; 95% CI: 979-262k; n=10), were more sensitive than TCL (median AUC=956k; 95% CI 1151-553k; n=15) (Figure 1A). Among TCL, cutaneous T lymphoma cell lines were the most sensitive (Figure 1B). Compared to idelalisib, IOA showed similar in vitro antiproliferative activity in ten cell lines derived from MZL, DLBCL and MCL (Figure 2). In diffuse large B-cell lymphoma (DLBCL; n=2) and MCL (n=2) cell lines, IOA induced apoptosis and subG0/G1 accumulation already after 48h at 1µM concentration (Figure 3).

IOA sensitivity correlated with PIK3CD RNA expression in all cell lines (R=-0.32; p=0.014), as for idelalisib (R=-0.45; p=0.053) but not for copanlisib (R<0.1; p=0.693) (Figure 4). In cells derived from B-cell lymphoma, only IOA-244 correlated with PIK3CD (R=-0.42; p=0.005; idelalisib R=0.1; p=0.992; copanlisib R<0.1; p=0.73). Transcriptomic analysis by RNA-seq revealed that IOA (5µM; 24, 48, 72h; MCL SP53 cell line) downregulated BCR, MYD88, NF-κB and anti-proliferative activity was assessed by MTT assay at 72h. Apoptosis and cell cycle were assessed by FACS. Poly-A production by Annexin V/PI staining followed by FACS acquisition were assessed after 24h of IOA-244-treated cell lines are shown as a continuous line, idelalisib-treated cell lines are shown in a dashed line. The most down-regulated transcripts (n=212; abs.fold change>2, adj.p<0.05) included oncogenes (CCND2, TOX, AXL, SGK1, VEGFA) and immune-related factors (CCL22, CCL4, CCR1, CXCR3, CSF1, IL2RB, TNFRSF9, SLAMF7, TNF) (Table 1). The up-regulated (n=188) included proapoptotic factors (HRK, BIK), tumor suppressors (GADD45A, TP63, BACH2), and immune-related factors (CXC4R, CTLA4).

CONCLUSIONS

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Table 1. Down- and up-regu-lated transcripts in B cell lines treated with IOA (24h) at 1µM and 72h. Representation genes dereg-ulated after 24h and 72h treat-ment. Log fold change (logFC) meta -value and p values related at each statisti-cal test is shown below.

Figure 1. Activity of IOA-244 on lymphoma cell lines, two diffuse large B cell lympho-mas (MCL, MZL, n=15) and 2 mantle cell lymphoma (SP53, Z138). Apoptosis in-duction by Annexin V/PI staining followed by FACS acquisition were assessed after 24h of IOA-244-treated cell lines are shown as a continuous line, idelalisib-treated cell lines are shown in a dashed line. The most down-regulated transcripts (n=212; abs.fold change>2, adj.p<0.05) included oncogenes (CCND2, TOX, AXL, SGK1, VEGFA) and immune-related factors (CCL22, CCL4, CCR1, CXCR3, CSF1, IL2RB, TNFRSF9, SLAMF7, TNF) (Table 1). The up-regulated (n=188) included proapoptotic factors (HRK, BIK), tumor suppressors (GADD45A, TP63, BACH2), and immune-related factors (CXC4R, CTLA4).