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Abstract 273

The novel aza-anthracenedione pixantrone has synergistic pre-clinical activity when combined with targeted agents in diffuse large B-cell lymphoma (DLBCL)

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INTRODUCTION AND RESULTS

Introduction: DLBCL is the commonest lymphoma and at least one quarter of patients still present with a refractory disease or relapse after first line chemotherapy. Pixantrone (Pix) is an aza-anthracenedione with reduced cardiotoxicity, which has received a conditional marketing approval in the E.U. as a monotherapy for the treatment of adults with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphomas. Here, we evaluated the pre-clinical activity of Pixa in combination with a series of additional anti-lymphoma drugs.

Results: Pix was active as single agent in DLBCL cell lines [median IC50 (50%-inhibitory concentration) at 72 h, 175 nM (95%, C.I., 35-245)] (Figure 1). Synergism was observed with the combination of Pix with ibrutinib (median CIndex across all the cell lines = 0.6, 95%, C.I., 0.51-0.74), idelalisib (median CIndex = 0.7, 95%, C.I., 0.63-0.83) and lenalidomide (median CIndex = 0.78, 95%, C.I., 0.71-0.84) (Table 1). Pix/ibrutinib combination was synergistic in 3/3 ABC DLBCL cell lines (Figure 2, Table 2). Pix/idelalisib combination was synergistic in 3/4 cell lines and additive in the remaining one. Synergism was observed in 2/5 cell lines when Pix was combined with rituximab. An additive effect was observed in 3/4 cell lines exposed to Pix/bendamustine. Pix and vorinostat were synergistic in 1/4 and additive in 1/4. None of the two ABC-DLBCL cell lines benefited from exposure to concomitant Pix plus bortezomib.

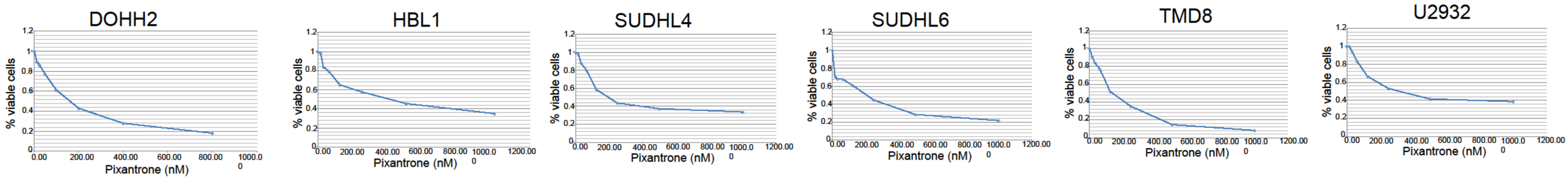

Figure 1. Proliferation curves of six DLBCL cell lines treated with single drug Pixantrone for 72h [median IC50 at 72 h, 175 nM (95%, C.I., 35-245)]

Second drug	Median CI	95% C.I
Bendamustine	1.03	0.98-1.13
Bortezomib*	1.25	0.98-1.5
Ibrutinib*	0.60	0.51-0.74
Idelalisib	0.70	0.63-0.83
Lenalidomide*	0.78	0.71-0.84
Vorinostat	0.99	0.94-1.07
Rituximab	0.92	0.79-1.06

*, only in ABC-DLBCL

Table 1. Combination index values obtained for pixantrone combined with a second drug in DLBCL cell lines. CI, Cindex; C.I. confidence interval.

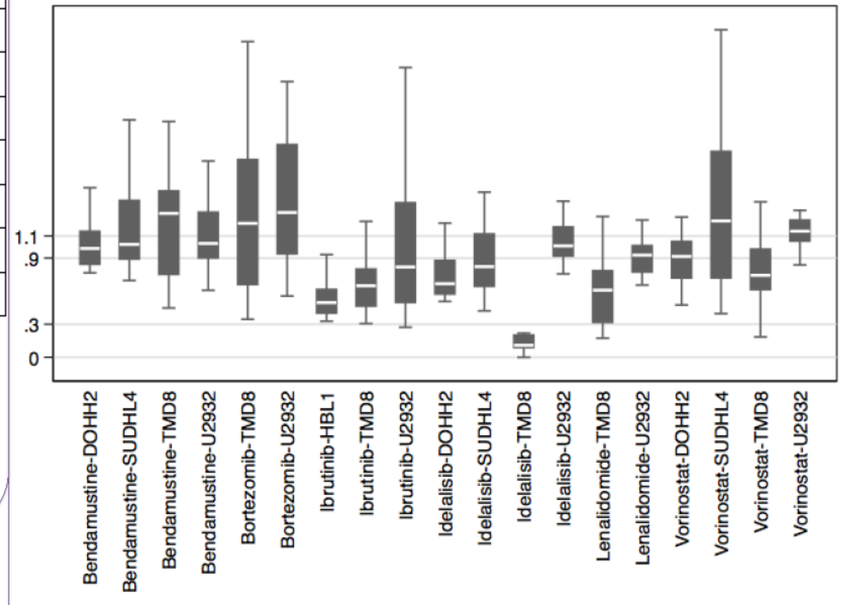

Figure 2. Pixantrone combinations in DLBCL cell lines: box-plots of the CI values obtained in individual cell lines. Y-axis: median Cindex. Outlier dots are excluded from the graph. In each box-plot, the line in the middle of the box represents the median and the box extends from the 25th to the 75th percentile (interquartile range, IQ); the whiskers extend to the upper and lower adjacent values (i.e., 1.5 IQ); outside values have been omitted from the figure.

DLBCL subtype	Cell line	Second drug	Median CI	95% C.I
GCB-DLBCL	DOHH2	Bendamustine	0.98	0.90-1.08
GCB-DLBCL	SUDHL4	Bendamustine	1.02	0.93-1.21
ABC-DLBCL	TMD8	Bendamustine	1.3	0.87-1.45
ABC-DLBCL	U2932	Bendamustine	1.03	0.95-1.24
ABC-DLBCL	TMD8	Bortezomib	1.21	0.85-1.6
ABC-DLBCL	U2932	Bortezomib	1.31	0.97-1.82
ABC-DLBCL	HBL1	Ibrutinib	0.50	0.45-0.58
ABC-DLBCL	TMD8	Ibrutinib	0.65	0.49-0.79
ABC-DLBCL	U2932	Ibrutinib	0.82	0.7-1.35
GCB-DLBCL	DOHH2	Idelalisib	0.67	0.59-0.82
GCB-DLBCL	SUDHL4	Idelalisib	0.82	0.71-0.92
ABC-DLBCL	TMD8	Idelalisib	0.11	0.09-0.18
ABC-DLBCL	U2932	Idelalisib	1.01	0.96-1.13
ABC-DLBCL	TMD8	Lenalidomide	0.61	0.39-0.72
ABC-DLBCL	U2932	Lenalidomide	0.93	0.83-1.01
GCB-DLBCL	DOHH2	Rituximab	0.79	0.74-0.9
GCB-DLBCL	OCILY19	Rituximab	>3	Min. >3
GCB-DLBCL	SUDHL6	Rituximab	>3	Min. >3
ABC-DLBCL	TMD8	Rituximab	0.74	0.63-0.79
ABC-DLBCL	U2932	Rituximab	>3	Min. >3
GCB-DLBCL	DOHH2	Vorinostat	0.92	0.77-0.99
GCB-DLBCL	SUDHL4	Vorinostat	1.24	0.91-1.63
ABC-DLBCL	TMD8	Vorinostat	0.74	0.63-0.92
ABC-DLBCL	U2932	Vorinostat	1.14	1.09-1.18

Table 2. Combination index values obtained for Pix combined with a second drug in DLBCL cell lines: data per individual cell line. CI, Cindex; C.I. confidence interval.

Material and Methods

DLBCL cell lines derived from activated B-cell like (ABC) DLBCL (U2932, TMD8, HBL1), and from germinal center B-cell (GCB) DLBCL (DOHH2, SU-DHL-4, OCI-Ly19) were studied. Pix was used in combination with: bendamustine, ibrutinib, idelalisib, lenalidomide, rituximab, vorinostat, bortezomib. Due to the mechanism of action, lenalidomide, bortezomib and ibrutinib were evaluated only in ABC-DLBCL cell lines. Cell lines were exposed (72 h) to increasing Pix doses alone or in combination with increasing doses of other agents, followed by MTT assay. The Chou-Talalay combination index (CIndex) was estimated using the Synergy R package: CI between 0.9 1.1 defined an additive effect; CI < 0.9, synergism; CI >1.1, no benefit.

CONCLUSIONS

Positive results were obtained when combining Pix with different drugs.
The combinations with the BTK inhibitor ibrutinib or with the PI3K-delta inhibitor idelalisib gave the best results and are worth of further studies at pre-clinical and clinical level.

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