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The targeted cytotoxic prodrug, AQ4N, has anti-tumor efficacy in L1210, P388 murine leukemia and Namalwa human lymphoma models

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Background

- AQ4N (banoxantrone) is a prodrug of a potent topoisomerase II inhibitor, AQ4
- Systemic toxicity of AQ4N is minimized due to lack of systemic bioreduction to AQ4
- AQ4N targets lymphatic tissues in vivo causing atropy
- AQ4N is being studied in human Phase I studies in the US and Europe
- AQ4N is active in Namalwa human lymphoma and L1210 and P388 murine leukemia cell lines as follows:

Tumor	Type	AQ4 (IC50)	AQ4N (IC50)*	Dox
Namalwa	Burkitt lymph	0.2 nM	400 nM	7.4 nM
P388	CLL (mouse)	10 nM	31.5 μM	0.1 μM
L1210	ALL (mouse)	1.2 nM	0.6 μM	50 nM

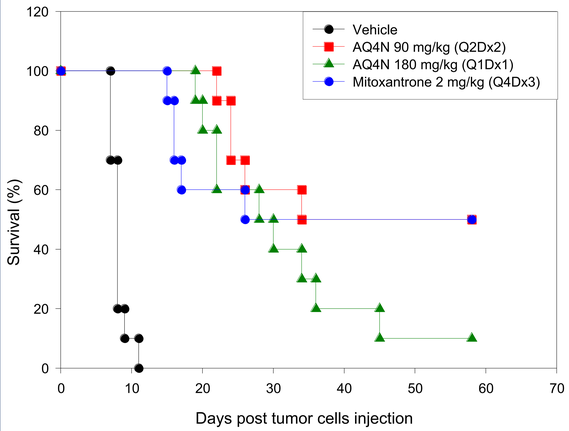
*All studies done under normoxic conditions only

Methodology

- The L1210 and P388 murine leukemia models were developed in DBA/2 mice (10-11 mice/group). Tumor inoculation was performed intraperitoneally (ip) on day 0, using 1 x 10^5 cells for L1210 and 1 x 10^6 cells for P388. Treatment was initiated ip on day 1, and efficacy was measured as percent survival. Treatment was compared with the standard agent, mitoxantrone.
- The Namalwa human lymphoma xenograft model was developed in nude mice (8-10 mice/group). Tumors were implanted subcutaneously. Drug treatment was initiated intravenously (iv) when established tumors were approximately 50-100 mm^3 in size. Anti-tumor efficacy was measured as tumor growth inhibition when control tumors reached appropriate size. Efficacy of AQ4N was compared to that of the standard agent, mitoxantrone.

Survival Benefit in Leukemia Models

AQ4N treatment yields long term survivors in L1210 leukemia model



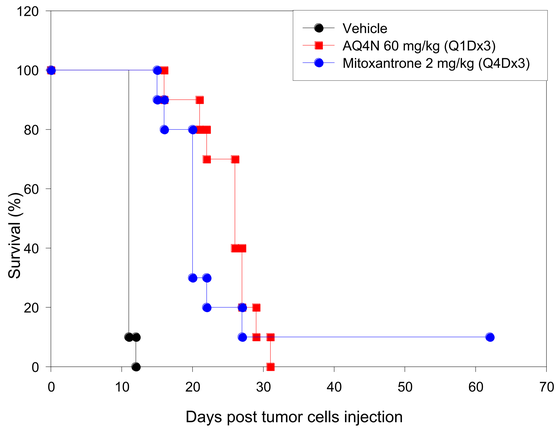
Mean Survival Time (days)

- Vehicle: 8.1 ± 1.2
- AQ4N (90 mg/kg q2dx2): 42 ± 17
- Mitoxantrone(2mg/kg q4dx3): 38 ± 21

Long term Survivors

- Vehicle: 0/10
- AQ4N (90 mg/kg q2dx2): 5/10
- Mitoxantrone(2mg/kg q4dx3): 5/10

AQ4N treatment provides good survival benefit below MTD in P388 leukemia model



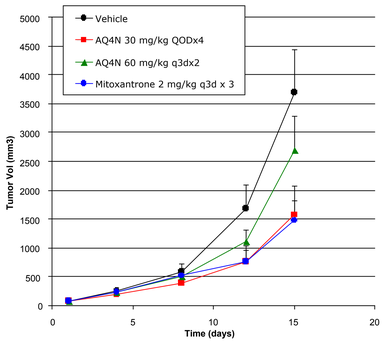
Mean Survival Time (days)

- Vehicle: 11.1 ± 0.2
- AQ4N (60 mg/kg qdx3): 25 ± 4.3
- Mitoxantrone(2mg/kg q4dx3): 24 ± 14

N=10-11 per group; data reproduced in 2 independent studies

Significant Tumor Growth Inhibition

Significant anti-tumor efficacy in Namalwa lymphoma xenograft model



Tumor Growth inhibition

- AQ4N (30 mg/kg qod x4): 58%
- Mitoxantrone(2mg/kg q3d): 60%

P<0.05 vs. vehicle

Summary

- AQ4N treatment results in significant anti-tumor efficacy in three lymphoid tumor models, L1210, P388, Namalwa.
- In L1210 leukemia, AQ4N treatment resulted in 575% increased survival with 5/10 long term survivors.
- In P388 leukemia, AQ4N treatment resulted in 240% increased survival, similar to the standard agent mitoxantrone.
- In Namalwa lymphoma, AQ4N treatment resulted in significant tumor growth inhibition of 58%, again similar to mitoxantrone.
- AQ4N monotherapy in these models may be direct or indirect through AQ4; mechanistic studies are planned.

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