Anticancer effects obtained against A20 lymphomas following treatment with LTX-315 (Oncopore™) in combination with low-dose cyclophosphamide

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Background

The need for new and improved anticancer therapies is imperative, with an increased focus on immunotherapy and the combination of different treatments to achieve an additive anticancer effect and maximize the following immune engagement and activation.

LTX-315 (Oncopore™) is a novel oncolytic peptide derived from the naturally occurring host defense peptide, bovine lactoferricin. By adopting an amphipathic helical structure, LTX-315 interacts electrostatically with the anionic components of negatively charged cancer cell membranes. LTX-315 induces a destabilization and disruption of the cancer cell membrane, causing cellular lysis and a subsequent release of endogenous cellular content and danger signals.

Low-dose cyclophosphamide has been shown to enhance immune responses, mostly through the inhibition of immune-suppressive cells such as MDSCs and Tregs, while simultaneously increasing the numbers of CD4+ and CD8+ T cells in the spleen of the host.

Aim

To investigate the anticancer effects of LTX-315 following intralesional administration in combination with low-dose cyclophosphamide against the A20 mouse lymphoma model.

Results

Fig. 2 - LTX-315 induces complete regression of palpable A20 tumors following intralesional administration in combination with low-dose cyclophosphamide

Mechanism of action

A proposed mechanism of action model for intralesional treatment with LTX-315

Conclusions

• LTX-315 induced complete regression of syngeneic A20 lymphomas when combined with low-dose cyclophosphamide.

• Intralesional treatment with LTX-315 in combination with low-dose cyclophosphamide provided local tumor control followed by systemic protective immune responses.

• LTX-315 has the potential to be used as a novel immunotherapeutic agent in combination with already existing anticancer therapies.

• A phase 1/2a study is in progress with LTX-315.

Experimental setup

LTX-315

Fig. 1 - Structural representations of LTX-315

Chemical structure of LTX-315 (top) and helical wheel representations as well as a secondary structure (bottom). Cationic residues are in blue and aromatic residues in grey.

Fig. 3 - LTX-315 treatment combined with low-dose cyclophosphamide resulted in protective systemic immune responses against A20 lymphomas

Fig. 4 - A proposed mechanism of action model for intralesional treatment with LTX-315

Palpable A20 lymphomas were injected intralesionally with sterile 0.9% NaCl (vehicle controls) or with 1 mg LTX-315. Animals were injected intraperitoneally with 2 mg CY or with 2 mg CY i.p. in combination with 1 mg LTX-315 i.t. The survival curves are represented in (p < 0.0001).

Naive control animals were inoculated with 5 x 10^6 A20 lymphoma cells and the tumor growth was compared to the tumor growth in animals previously cured by LTX-315 in combination with low-dose cyclophosphamide. The survival curves are represented in (p.< 0.0001).