Mitochondrial metabolism impairment induced by oxazolidinones at clinically-relevant concentrations: studies with two human megakaryocytic cell lines (UT7-WT and UT7-MPL)

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Background and Aim

Oxazolidinone antibiotics inhibit protein synthesis in bacteria as well as in mitochondria [1-3]. The latter inhibition has been associated with severe side effects like myelosuppression [4] especially thrombocytopenia.

Our aim was to compare linezolid (LZD) and tedizolid (TZD) for their inhibitory effect on the expression and activity of cytochrome c-oxidase and on mitochondrial respiration in two different megakaryocytic cell lines.

Materials & Methods

Cells: UT7-WT (wild type: human acute megakaryoblastic leukemia cells) [5] and UT7-MPL (transfected by the pMex-res-GFP HA huMPL vector and expressing a thrombopoietin receptor [TpR or c-MPL]) [6].

Treatments: incubation with LZD or TZD at increasing total concentrations or at their total C\textsubscript{t} treated as per the corresponding EU-approved label (see [3]).

Assays (see [3] for details):
- Cytox I expression (subunit of cytochrome c-oxidase; encoded by the mitochondrial genome). Western blot analysis with Tom 20 (encoded by the nuclear genome) as loading control.
- Cytochrome c-oxidase activity: measure of the rate of oxidation of reduced cytochrome c (decrease of OD\textsubscript{550}).
- Basal mitochondrial oxygen consumption rate (OCR) and/or non-profit institutional grants to the authors. TM and SC are is employees of UCL. VLP was provided as coauthor.

Results

1. Cytox I expression and cytochrome c-oxidase activity: concentration-effect

2. Cytox I expression: time-effect at C\textsubscript{max} (UT7-WT cells)

3. Mitochondrial metabolic activity after 72h at C\textsubscript{max}

4. Recovery (cytochrome c-oxidase) upon drug withdrawal

Both LZD and TZD inhibit the expression of a protein encoded by the mitochondrial genome (Cytox I) and the activity of a key enzyme of complex IV in mitochondria (cytochrome c-oxidase) at therapeutically pertinent concentrations.

Cytochrome c-oxidase activity (at 72h) is significantly decreased in both cell lines.
- Basal mitochondrial OCR is reduced in U7-MPL but not in U7-WT.
- Spare capacity (sparing the ability of cells to meet an increased energy demand [3]) is reduced in both cell lines.

The lack of recovery upon drug withdrawal in UT7-MPL but not in U7-WT or in other cell lines not part of the megakaryocyte lineage (see [3]) might explain the preferential and therapeutically limiting effect of oxazolidinones on platelets levels in patients [4,7].

Main points and Discussion

- Both LZD and TZD cause, at clinically-relevant concentrations, an impairment of the expression of CYTox I, an inhibition of the activity of cytochrome c-oxidase, and a decrease of the spare capacity of the mitochondrial respiration in human megakaryocytic cell lines, with less differentiated cells being only slightly more susceptible.
- TZD is, globally, a more potent inhibitor than LZD in cells continuously exposed to either drug.
- The lack of recovery upon drug withdrawal in UT7-MPL but not in U7-WT or in other cell lines not part of the megakaryocyte lineage (see [3]) might explain the preferential and therapeutically limiting effect of oxazolidinones on platelets levels in patients [4,7].

Acknowledgments and Transparency Declaration

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References


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