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Short Communication

Prolonged inhibition and incomplete recovery of mitochondrial function in oxazolidinone-treated megakaryoblastic cell lines

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ABSTRACT

Thrombocytopenia is commonly seen in patients receiving linezolid for >14 days. Linezolid is a reversible inhibitor of mitochondrial function in various cell types. This study investigated the inhibitory effects of linezolid and tedizolid, and their potential recovery on (i) CYTox I expression (subunit I of cytochrome *c*-oxidase; encoded by the mitochondrial genome), (ii) cytochrome *c*-oxidase activity and (iii) mitochondrial respiration (Seahorse bioanalysis) in two megakaryocytic cell lines [UT-7 WT (human acute megakaryoblastic leukaemia cells) and UT-7 MPL (transduced to express the thrombopoietin receptor)]. Cells were exposed to linezolid (0.5–25 mg/L) or tedizolid (0.1–5 mg/L) for up to 5 days and recovery followed after drug removal. Both oxazolidinones caused concentration- and time-dependent inhibition of CYTox I expression, cytochrome *c*-oxidase activity and mitochondrial spare capacity. On electron microscopy, mitochondria appeared dilated with a loss of cristae. Globally, tedizolid exerted stronger effects than linezolid. While CYTox I expression recovered completely after 6 days of drug washout, only partial (linezolid) or no (tedizolid) recovery of cytochrome *c*-oxidase activity, and no rescue of mitochondrial spare capacity (after 3 days) was observed. Thus, and in contrast to previous studies using a variety of cell lines unrelated to megakaryocytic lineages, the inhibitory effects exerted by oxazolidinones on the mitochondrial function of megakaryoblastic cells appear to be particularly protracted. Given the dynamics of platelet production and destruction, these results may explain why oxazolidinone-induced thrombocytopenia is one of the most common side effects in patients exposed to these antibiotics.

1. Introduction

Oxazolidinones are the latest class of antibiotics with a novel mode of action to reach widespread clinical use. They inhibit bacterial protein synthesis by binding to the ribosomal 50S subunit and impairing formation of the initiation complex [1]. They are active against most multi-resistant staphylococci and enterococci of clinical origin [2]. Due to their excellent oral bioavailability, they are often selected for early discharge of patients. Unfortunately, treatment with linezolid (the first approved oxazolidinone) for >14 days and/or in patients with renal insufficiency is frequently associated with haematological side effects, with thrombocytopenia affecting up to 30% of patients [3–5]. Although approximately two- to eight-fold more potent than linezolid [2], tedizolid was reported to cause less thrombocytopenia based on the results of dose-escalating phase I trials and of fixed-dose, 6-day-treatment phase III clinical trials [6]. However, this has been challenged based on data from the Food and Drug Administration registry covering 18 months clinical use of tedizolid [7].

Given the similarity between bacterial and mitochondrial ribosomes, oxazolidinones also bind to mitochondrial ribosomes, impair the expression and synthesis of mitochondrial proteins encoded by the mitochondrial genome [8,9], and inhibit the activity of cytochrome *c*-oxidase and mitochondrial oxidative activity [9]. These effects are rationalized by structural similarities between

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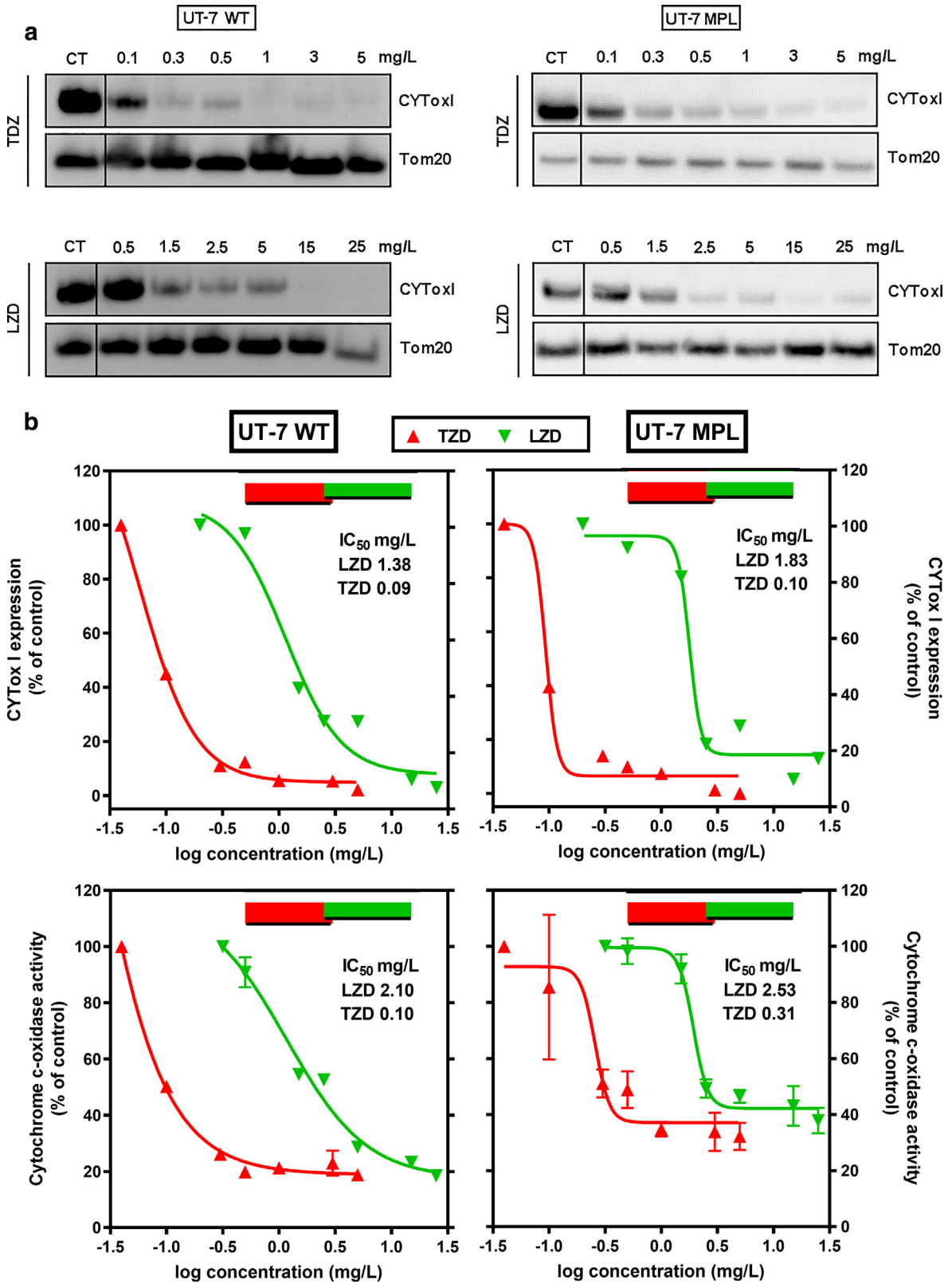

Fig. 1. Influence of increasing concentrations of tedizolid (TZD) and linezolid (LZD) on CYTox I protein expression and cytochrome *c*-oxidase activity of UT-7 WT and UT-7 MPL cells incubated for 5 days. (A) Western blots of CYTox I and Tom 20 (used as a loading control) in mitochondrial fractions with controls (vehicle only) on the left and increasing concentrations (from 0.1 to 5 mg/L and from 0.5 to 25 mg/L for TZD and LZD, respectively). (B) Quantitative measurements: change in cytochrome *c*-oxidase activity presented as mean ± standard deviation (SD) of triplicates in a single experiment (when not visible, the SD bars are smaller than the symbols); for both graphs, the abscissa is expressed as the $\log_{10}$ of the concentration of each drug. IC_{50} values (calculated from the Hill functions) for UT-7 WT: upper panel (LZD 1.38 mg/L or 4.09 μM; TZD 0.09 mg/L or 0.24 μM); lower panel (LZD 2.10 mg/L or 6.23 μM; TZD 0.1 mg/L or 0.27 μM); and for UT-7 MPL: upper panel (LZD 1.83 mg/L or 5.43 μM; TZD 0.1 mg/L or 0.27 μM); lower panel (LZD 2.53 mg/L or 7.51 μM; TZD 0.31 mg/L or 0.83 μM). The coloured rectangles in the top graphs refer to the interval between the C_{min} and C_{max} values commonly observed in serum of humans (0.5–3 mg/L and 2–15 mg/L, respectively) receiving conventional doses of TZD (200 mg) or LZD (600 mg).

bacterial and mitochondrial ribosomes, with common binding sites for oxazolidinones [10]. Most notably, tedizolid possesses additional interactions with the oxazolidinone target site in bacterial ribosomes [11]. It also causes higher inhibition than linezolid for (i) mitochondrial protein synthesis in isolated cardiac mitochondria [12], and (ii) CYTox I expression (a protein encoded by the mitochondrial genome) and cytochrome *c*-oxidase activity in human HL-60 promyelocytes and THP-1 monocytes [9]. These cell lines, however, have no or only a weak link to the megakaryocytic lineage, drawing into question their predictive value to assess the impact of oxazolidinones on platelet precursors. In this context, this study examined the impact of linezolid and tedizolid on the expression of CYTox I and on cytochrome *c*-oxidase activity in UT-7 cells, considered as a useful in-vitro surrogate of megakaryoblasts. They were compared with UT-7 cells transduced to express a functional thrombopoietin (TPO) receptor, corresponding to more differentiated megakaryocytes.

2. Methods

Linezolid (potency 99.2%) was obtained as RX-0366-00-005 from Rib-X Pharmaceuticals (presently Melinta Therapeutics, New Haven, CT, USA), and tedizolid (potency 101.4%) as microbiological standard from Trius Pharmaceuticals (San Diego, CA, USA) and thereafter from Cubist Pharmaceuticals GmbH (Zürich, Switzerland), both now parts of Merck & Co. (Kenilworth, NJ, USA). Stock solutions were prepared in DMSO, and diluted to bring the final DMSO concentration in the culture fluid to 0.5% (no cytotoxicity observed). Granulocyte-macrophage colony-stimulating factor (GM-CSF) and human TPO were obtained from Miltenyi Biotec GmbH, Bergisch Gladbach, Germany.

UT-7 WT human acute megakaryoblastic leukaemia cells were obtained from the German Collection of Microorganisms and Cell Cultures (Deutsche Sammlung von Mikroorganismen und Zellkulturen, Braunschweig, Germany) [13]. UT-7 MPL cells [14] are UT-7 WT cells transduced with viral particles derived from packaging cell lines transfected with pMex-ires-GFP HA huMPL vector that code for the human TPO receptor (TpoR or c-MPL). These cells were grown in MEM-alpha GlutaMAX medium (Gibco-Life Technologies, Thermo-Fisher Scientific Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (Gibco-Life Technologies) and GM-CSF at 10 ng/mL for UT-7 WT, or TPO at 10 ng/mL for UT-7 MPL. They were incubated at 37°C in a 5% CO_2–air atmosphere. Proliferation was evaluated using an automated cell counter (Beckman Coulter Life Science, Indianapolis, IN, USA).

Mitochondria-enriched preparations were obtained as described previously [9]. Protein concentrations were measured using a bicinchoninic acid assay (BCA Protein Assay Reagent, Pierce, Thermo Fisher, Waltham, MA, USA), with equal amounts of proteins separated by NuPAGE using 10% Bis-Tris precasted gels. The following primary antibodies were used: mouse anti-cytochrome *c*-oxidase subunit I (CYTox I) monoclonal antibody (Anti-OxPhos Complex IV Subunit I Monoclonal Antibody; Invitrogen cat. no. 459600) at 0.4 µg/mL and rabbit anti-Tom20 polyclonal antibody (Invitrogen cat. no. PA5-39247) at 0.2 µg/mL. Secondary antibodies (rabbit anti-mouse IgG (Invitrogen cat. no. A27025) and goat anti-rabbit IgG antibody (Invitrogen cat. no. A27036) were used at a concentration of 0.4 µg/mL. Band intensity was quantified on membranes scanned using Chemiluminescence Imaging-Fusion PULSE apparatus (Analis, Namur, Belgium) with Image J software (National Institutes of Health, Bethesda, MD, USA; available from https://imagej.nih.gov/ij/).

Cytochrome *c*-oxidase activity was assayed on sonicated cells as described previously [9] after exposure to 0.2 % digitonin, and calculated as the slope of the change in absorption of reduced cytochrome *c* over time after logarithmic linearization, normalized based on the protein content of the cell lysate, determined by Lowry's method.

For mitochondrial oxygen consumption rate measurements, cells were collected by low speed centrifugation, and resuspended at a suitable dilution in Dulbecco′s modified Eagle′s medium (Sigma-Aldrich cat. no. D5030, Sigma Aldrich, St Louis, MO, USA) supplemented with 1.85 g/L NaCl, 10 mM D-glucose and 2 mM L-glutamine, and seeded in a poly-L-lysine-coated (Sigma-Aldrich cat. no. P6282) Seahorse XF96 V3 PS cell culture microplate (Agilent cat. no. 101085-004, Agilent Technologies, Santa Clara, CA, USA) at densities of 250,000 cells/well. Oxygen consumption rate (OCR) and its various stages (basal respiration, ATP-linked respiration, spare capacity and maximal respiration) were measured on a Seahorse XF96 analyzer as described in [9]. Data were normalized by cell count using a SpectraMax i3 plate imager (Molecular Devices, Sunnyvale, CA, USA) and SoftMax Pro software (Molecular Devices).

Preparation of samples for electron microscopy was performed as described previously [9].

Products not described above were obtained from Sigma-Aldrich or Merck KGaA (Darmstadt, Germany).

Curve fitting and statistical analyses were performed using GraphPad Prism Version 8.1.1. (330) and GraphPad InStat Version 3.10 for Windows (GraphPad Software, Inc., San Diego, CA, USA, www.graphpad.com).

3. Results

3.1. Oxazolidinones at increasing concentrations inhibit CYTox I expression and cytochrome c-oxidase activity

CYTox I (one of 13 proteins of the mitochondrial respiratory chain encoded by the mitochondrial genome) expression was examined in UT-7 WT and UT-7 MPL megakaryocytic cell lines incubated for 5 days with linezolid or tedizolid over a wide range of concentrations chosen to cover that of clinically relevant concentrations (see Fig. 1). The expression of Tom20, a translocase from the outer mitochondrial membrane encoded by the nuclear genome, was measured in parallel. While the expression of Tom20 was not affected by oxazolidinones, both drugs inhibited CYTox I expression in a concentration-dependent manner. The protein became almost undetectable for concentrations of linezolid >15 mg/L and of tedizolid of 0.3 mg/L (Fig. 1A). Calculations of the concentration of antibiotic causing 50% activity inhibition (IC_{50}) showed that tedizolid was 17–20 times more potent as an inhibitor than linezolid in UT-7 WT and UT-7 MPL cells, respectively [Fig. 1B (upper panel); see caption for IC_{50} values].

The enzymatic activity of cytochrome *c*-oxidase was measured in parallel in the same conditions [Fig. 1B (lower panel)]. Both oxazolidinones induced a concentration-dependent decrease in enzymatic activity, with tedizolid being more potent than linezolid (9 to 24 times in UT-7 MPL and UT-7 WT, respectively).

UT-7 WT cells were therefore slightly more susceptible to linezolid treatment than UT-7 MPL cells (1.3-fold decrease in CYTox I protein expression and 1.2-fold decrease in enzyme activity). For tedizolid, the ratio of IC_{50} values for UT-7 WT to UT-7 MPL was approximately 1 for CYTox I expression but 3 for enzyme activity.

3.2. Influence of the time of incubation with oxazolidinones on CYTox I protein expression, cytochrome c-oxidase activity, mitochondrial respiration and ultrastructure

Changes in CYTox I protein expression were followed over time in cells exposed to a fixed concentration of both drugs corresponding to their human C_{max} (linezolid: 15 mg/L; tedizolid:

3 mg/L). Data are presented in Fig. 2A,B. Both drugs completely inhibited CYTox I protein expression after 72 h in UT-7 WT cells, as well as linezolid in UT-7 MPL cells. However, a residual activity of approximately 20% was observed in UT-7 MPL cells treated with tedizolid. In order to assess the potential functional impact of this decrease, cytochrome *c*-oxidase activity and mitochondrial respiration of UT-7 WT and UT-7 MPL cells were measured (Fig. 2C,D). Cells were incubated for 72 h at a concentration corresponding to the C_{max} of oxazolidinones, at which maximal inhibition of CYTox I expression was obtained. As shown in Fig. 2C, enzyme activity was significantly reduced to approximately 50–75% in both cell lines. Fig. 2D shows that basal mitochondrial OCR and spare capacity (i.e. the ability to increase mitochondrial OCR from a basal to a maximal level) were reduced by either oxazolidinone in UT-7 WT cells, while only spare capacity was impaired in UT-7 MPL cells. Typical images of mitochondria under control conditions and after incubation with oxazolidinones at their C_{max} for 72 h are shown in Fig. 2E. Mitochondria appeared less dense in UT-7 MPL cells than in their WT counterparts, with fewer cristae. In oxazolidinone-exposed cells, mitochondria were dilated in both cell types and harboured scarce, disorganized cristae.

3.3. Reversibility of the inhibition of CYTox I expression, cytochrome c-oxidase activity and mitochondrial spare capacity

Cells were treated for 72 h with oxazolidinones at their C_{max} (to obtain maximal inhibition of cytochrome *c*-oxidase subunit I

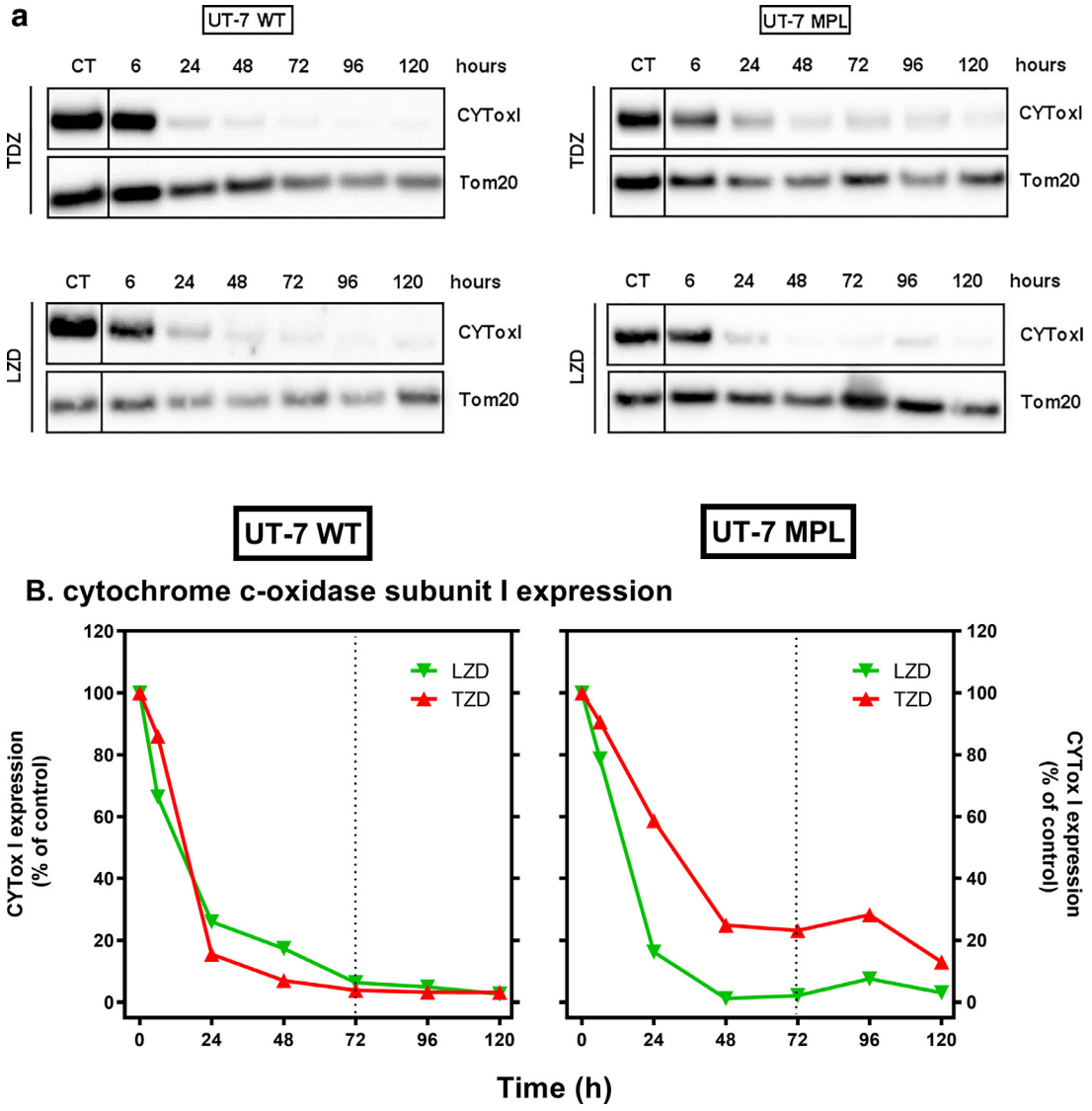

Fig. 2. Influence of time of incubation with linezolid (LZD) or tedizolid (TZD) on CYTox I expression, cytochrome *c*-oxidase activity, mitochondrial respiration and mitochondrial ultrastructure in UT-7 WT (left) and UT-7 MPL (right) megakaryocytes after 72 h of incubation. (A) Western blots of CYTox I and Tom 20 (used for normalization) in mitochondrial protein fractions, with controls (vehicle only) on the left and increasing times of incubation at a concentration corresponding to their peak (C_{max}) serum concentrations most commonly observed for each antibiotic (TZD: 3 mg/L; LZD: 15 mg/L) when administered to humans at conventional dosages (TZD: 200 mg; LZD: 600 mg) (B) Quantitative measurements (band density) of CYTox I: Tom 20 ratio (the vertical dotted line at 72 h refers to the time of incubation selected in further experiments). (C) Changes in cytochrome *c*-oxidase activity and (D) mitochondrial respiration in UT-7 WT and UT-7 MPL cells incubated for 72 h in control conditions (gray hatched bars) or in the presence of LZD (green hatched bars) or TZD (red hatched bars). Values are shown as percentage of control ± standard deviation of triplicates for cytochrome *c*-oxidase activity and as means of absolute values ± standard error of mean of six to eight wells for mitochondrial oxygen consumption. Statistical analysis: one-way analysis of variance with Dunnett's multiple comparison of each treatment vs control (not significant: $P>0.05$, $^{*}P<0.05$, $^{**}P<0.01$). (E) Morphological appearance of mitochondria in control and oxazolidinone-treated UT-7 WT and UT-7 MPL cells. Representative transmission electron micrographs of cells incubated for 72 h in control conditions or with LZD or TZD at the extracellular concentration corresponding to their human total C_{max}. Bars: 1 µm.

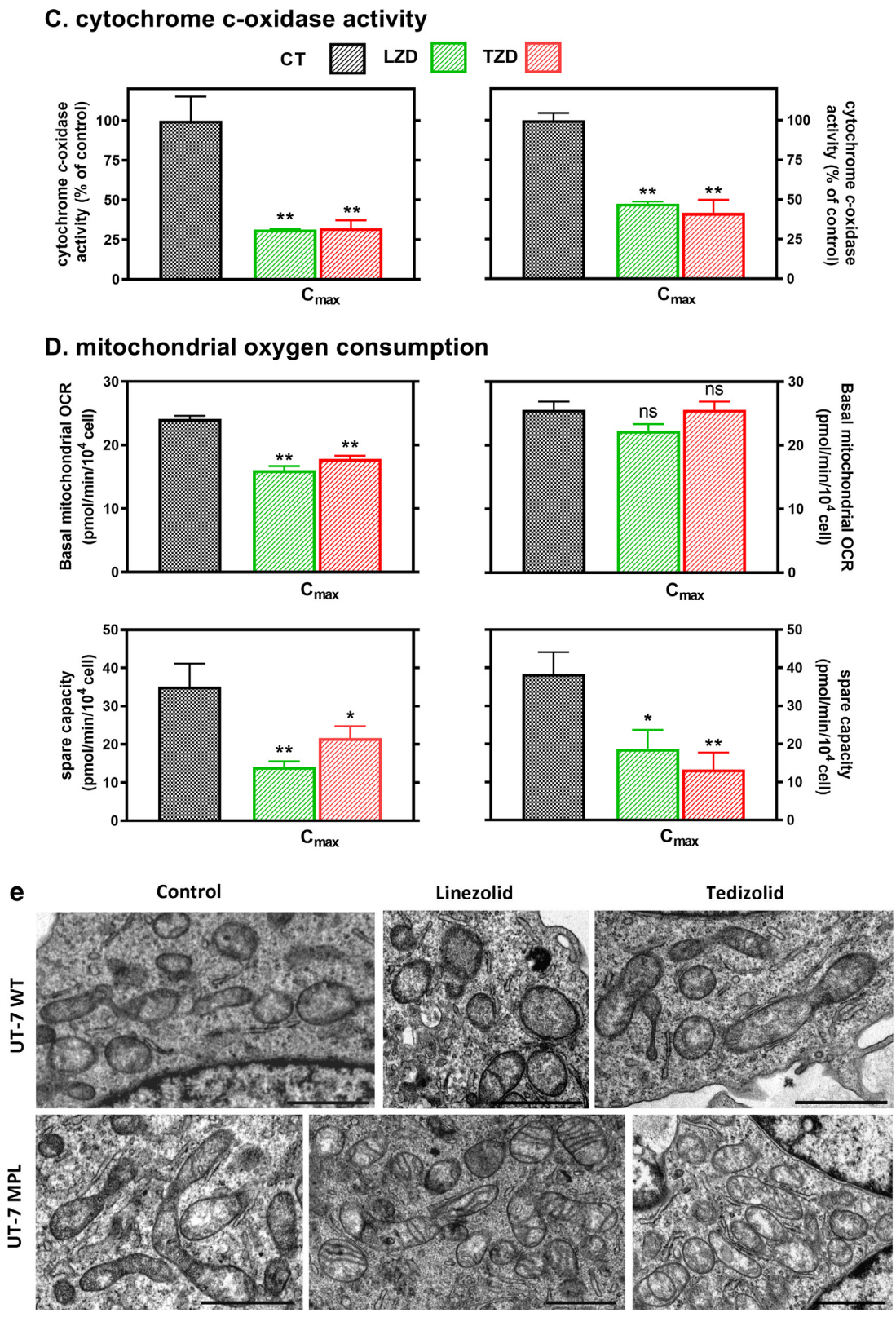

Fig. 2. Continued

expression) and then transferred to drug-free media for up to 144 h. CYTox I expression recovered completely in both cell lines after 72 h of washout (Fig. 3A,B), but this period of time was insufficient to completely restore cytochrome *c*-oxidase activity in both cell lines. Prolonging the washout period to 144 h allowed for increased recovery of enzyme activity after linezolid treatment but not after tedizolid treatment (Fig. 3C). This study also tested whether drug washout would allow for recovery of mitochondrial spare capacity, and found that it was variable but only partial in most cases after 3 days (data not shown).

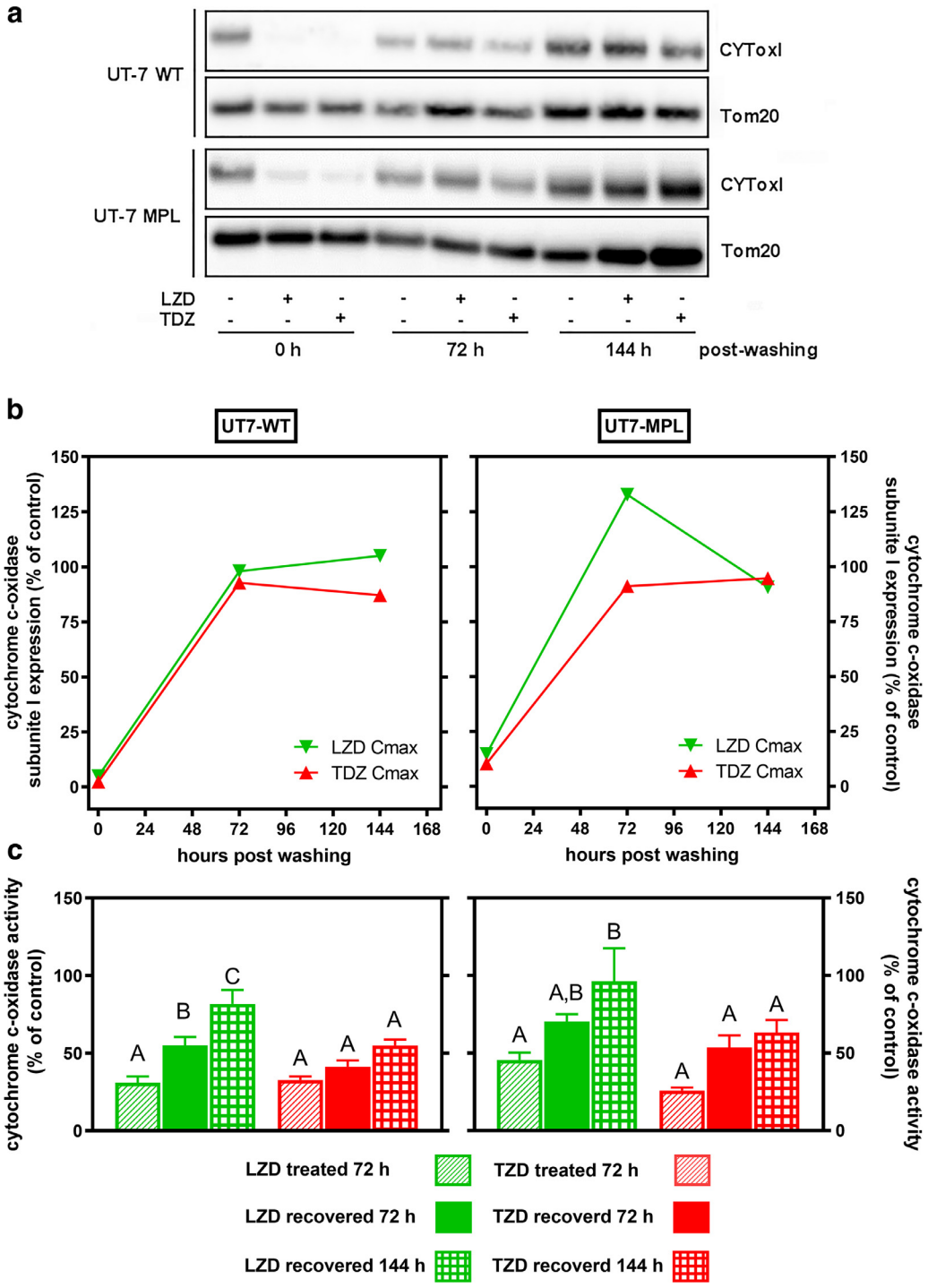

Fig. 3. Effect of oxazolidinones on CYTox I expression and cytochrome *c*-oxidase activity after drug removal. UT-7 WT and UT-7 MPL cells were incubated for 72 h with linezolid (LZD) and tedizolid (TZD), then transferred into drug-free medium for the next 72 or 144 h. (A) Western blot analysis of the expression of CYTox I and Tom 20 (used for normalization). (B) Quantitative measurement (CYTox I:Tom 20 band density ratio). (C) Recovery of cytochrome *c*-oxidase activity [mean ± standard error of mean of triplicates in two independent experiments (when not visible, the bars are smaller than the symbols)] for one concentration (C_{max}) of both antibiotics (treated, diagonally-hatched bars; LZD 15 mg/L, TZD 3 mg/L), followed by either 72 h (72 h recovery, plain bars) or 144 h in drug-free medium (144 h recovery, square-hatched bars). Statistical analysis (one-way analysis of variance with Tukey-Kramer post-test for multiple comparison of all pairs of columns): values with different letters are significantly different from each other ($P<0.05$).

4. Discussion

Inhibition of mitochondrial protein synthesis by oxazolidinones, due to the existence of common binding sites for oxazolidinones in bacterial and human mitochondrial ribosomes [10], has been reported in both preclinical and clinical studies [8,15]. It has been convincingly associated with impairment of mitochondrial oxidative metabolism in human promyelocytic (HL-60) and monocytic (THP-1) cell lines [9]. This study presents data using cell lines that are more directly related to platelet-generating cells *in vivo*, namely megakaryoblasts and megakaryocytes. The key observations were that (i) UT-7 cells are as susceptible as other cell lines to the inhibitory effects of oxazolidinones on key mitochondrial parameters, namely CYTox I expression (encoded by

mitochondrial genome), cytochrome *c*-oxidase activity and oxidative metabolism; (ii) but that some of these inhibitory effects, especially those caused by tedizolid, are less easily reversed compared with what has been observed with the cell lines examined to date. Interactions between oxazolidinones and bacterial ribosomes are non-covalent and, therefore, should be reversible. In UT-7 cells, CYTox I expression was readily reversed in oxazolidinone-free medium, but the recovery of cytochrome *c*-oxidase activity was slower and incomplete, especially in cells exposed to tedizolid. Of interest, the effects on UT-7 MPL cells, which are more differentiated megakaryoblasts/megakaryocytes and have a maximal TpoR cell-surface expression, were more pronounced than on UT-7 parental cells. Possibly, basal signalling by the TpoR itself might activate pathways that regulate mitochondrial size and components which are relevant for toxicity and recovery in the context of oxazolidinones. It can also be speculated that the perturbations induced by oxazolidinones on mitochondrial structure are so severe that they alter the correct assembly of the cytochrome *c*-oxidase complex. Cytochrome *c*-oxidase is made of 14 subunits, three of which (CYTox I, II and III) are encoded by the mitochondrial genome. Specific inhibition of their synthesis by oxazolidinones would create an imbalance between all the subunits necessary for cytochrome *c*-oxidase expression and activity [16], resulting in a disassembly of complex IV that may not be easily reversed. Also, it is known that phorbol-myristate-induced differentiation of megakaryocytes is accompanied by a reduction in their mitochondrial activity and alteration of mitochondrial ultrastructure (diminished matrix density, disorganized cristae) [17] reminiscent of what was observed in the present study for UT-7 cell lines when exposed to oxazolidinones. Mitochondrial fragmentation has been shown to occur during megakaryoblast differentiation, probably as a compensatory response to restore adequate mitochondrial function [17]. This may become impossible and result in irreversible loss of function if oxazolidinones are present. An increase in mitochondrial DNA content and RNA expression after linezolid therapy has also been suggested as a compensatory mechanism to prevent further damage [18]. Although calling for further studies, the present data may already identify megakaryocytes as a privileged target for expression of toxicity *in vivo*. The non-recoverable impairment of their mitochondrial functions would lead to progressive thrombocytopenia, as is observed in patients who then require another full round of megakaryoblast and megakaryocyte formation from haematopoietic precursors/stem cells before correcting for the platelet deficit. The dynamics of platelet formation and destruction would favour negative clinical effects. This is largely in line with the recent pharmacokinetic modelling approaches describing how oxazolidinones interfere with the whole process of megakaryocyte differentiation and platelet release [19].

Finally, tedizolid caused more extensive and sustained mitochondrial alterations than linezolid, even when comparing equitherapeutic concentrations. While this may describe an in-vitro reality (also observed with isolated mitochondria [20]), the clinical situation could be different since the conditions of use in registration clinical trials (dosages [200 mg for tedizolid vs. 600 mg for linezolid] and frequency of administration (once daily for tedizolid vs. twice daily for linezolid) as well as the extent of protein binding of tedizolid and linezolid are quite different (see discussion in [9] and [12]). Thus, true toxicity ranking will require more detailed comparative in-vitro studies, as well as more extensive clinical experience.

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Ethical approval: Not required.

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