biopsy the lesions and subsequently monitor her response to steroids with continuation of trastuzumab, since benefits of trastuzumab outweigh the risks of eczema.³

Conclusions We report the first case of trastuzumab therapy presenting with extensive infected pompholyx (dyshidrotic) eczema in a breast cancer patient. Although the patient described a history of a mild eczema five years previously, an acute flare while undergoing treatment could certainly be added to conditions at risk of flare during trastuzumab therapy until this is proven as a clear trastuzumab side effect through meta-analysis of multiple studies and a comprehensive dataset.

REFERENCES

- Baselga J, Cortés J, Kim SB, *et al*, CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;**366**:109–19. doi:10.1056/NEJMoa1113216
- Ana Maria Abreu-Velez, Frank J Pinto Jr, Michael S. Howard. Dyshidrotic eczema: relevance to the immune response *in situ*. *N Am J Med Sci* 2009;1:117–120. PMID: PMC3364640.
- Chang HR. Trastuzumab-based neoadjuvant therapy in patients with HER2-positive breast cancer. *Cancer* 2010;**116**:2856–67. doi:10.1002/cncr.25120

3 EVALUATION OF HO-1 INVOLVEMENT IN MELANOMA RESISTANCE TO BRAF INHIBITOR VEMURAFENIB

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Introduction The point mutation of the BRAF gene (BRAFV600E) is present in more than 50% of melanoma.

This mutation determinate the continuous activation of MAPK pathway, which favours cell survival and proliferation. Vemurafenib/PLX4032 (PLX4032) is an inhibitor of BRAFV600 used for the therapy of these tumours, but, after an initial positive response, in many cases a relapse of the disease occurs. HO-1 is the inducible form of heme oxygenase and overexpression is involved in the growth and resistance to therapy of different types of tumours. In this study we have evaluated the involvement of HO-1 in chemoresistance and angiogenesis of BRAFV600E primary melanoma cells.

Materials and methods We used a primary melanoma cell line, derived from a metastasis from a patient, and exposed cells to PLX4032 (1–10 µM). The role of HO-1 was studied by gene silencing or using the pharmacological inhibitor of HO-1 tinmesoporphyrin IX (SnMP-IX), a drug used to treat hyperbilirubinemia. Angiogenic potential was evaluated by using bovine aortic endothelial cells (BAEC) isolated in our laboratory.

Results Primary melanoma cells (MeOV-1) were exposed to 1–10 µM PLX4032 for 24 hour. MTT and Trypan blue assays showed a reduction in cell viability of 45% and immunoblot and qRTPCR analyses revealed a significant upregulation of HO-1 expression. HO-1 silencing or exposure to 10 µM SnMP-IX further decreased cell viability after exposure to PLX4032. Subsequently, we evaluated the angiogenic potential of melanoma cells. Medium derived from MeOV-1 cells, exposed to 10 microlar PLX4032, was used to treat BAEC seeded on Matrigel. Tube formation, branching and density were increased in comparison to BAEC exposed to the medium from untreated MeOV-1 cells. Interestingly, when BAEC were treated with conditioned medium from MeOV-1 cells and HO-1 was silenced, 10 µM PLX4032 showed a reduced ability to form tubes.

Conclusions These Results highlight an important role of HO-1 in favouring melanoma resistance to target therapy and angiogenesis.

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4 WHICH INTENSIVE CARE ANALYTICS ARE A WORTHWHILE INVESTMENT FOR DEVELOPERS? AN EARLY HEALTH TECHNOLOGY ASSESSMENT

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Introduction In intensive care (IC), monitoring data are continuously being collected. Unfortunately, this data is often not interpretable for clinicians and therefore goes unused. While advanced analytics can process this data to support improvements in patient care, developers ideally invest in those analytics that lead to the greatest health benefits or cost reductions. We explored the potential cost-effectiveness of three IC analytics.

Subjects and methods We assessed the cost-effectiveness of three applications: the early identification of catheter-related bloodstream infection (CRBSI), improved nutrition monitoring and identification of high driving pressure (HDP) in ventilated patients. The literature was used to populate the decision trees and patient data from a Greek IC were used for the nutrition and HDP estimates. We performed univariate, multivariate, and probabilistic sensitivity analyses.

Results Early identification of CRBSI reduced mortality and length of stay, thereby increasing quality-adjusted life-years (QALYs) (6.70 vs. 6.58) and reducing costs (€ 8183 vs. € 9,869); probability of CRBSI and the costs per IC day were key influencers of the ICER and the probability of dominance was 90%. Improved nutrition monitoring could increase nutrition adherence (0.37% vs. 0.03%) and decrease costs by reducing length of stay (€ 9988 vs. € 10,720). For HDP, benefits were limited, resulting in higher costs as well as minimal and highly uncertain health benefits.

Conclusions Developers should study the potential impact of the analytics they wish to develop before investing time and money. We illustrate that analytics for early identification of CRBSI and improved nutrition monitoring are worth further investment while identifying HDP may not be. The other factors that influence success besides health and financial benefits such as the competition and data access should be assessed.

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5 INVESTIGATING THE EFFECT OF CATECHOLAMINES ON ISCHAEMIA-INDUCED VENTRICULAR FIBRILLATION WHEN IN THE PRESENCE OF AN INTRAVENTRICULAR BALLOON

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Introduction Sudden cardiac death (SCD) is the greatest cause of cardiovascular disease-related mortality. Lethal ventricular

fibrillation (VF), arising from myocardial infarctions is the most prominent cause of SCD. The isolated rat heart is widely used to model ischaemia-induced VF owing to its ability to produce high baseline incidences of VF and the ability to regulate several known arrhythmogenic mediators. A model that allows concurrent assessment of VF and contractile function would halve animal requirements. Unfortunately, in Langendorff perfused rat hearts, IVB inflation inhibits the ability of regional ischaemia to elicit VF.¹ However, perfusion with catecholamines facilitates ischaemia-induced VF (I-IVF) in IVB-free hearts when risk of VF is low due to a small ischaemic territory.² Therefore, it was sought to overcome the IVB-induced VF suppression by perfusion with exogenous catecholamines: rendering a model in which the antiarrhythmic properties and the effects on heart dynamics a potential drug has could be assessed simultaneously. Here we tested whether catecholamines can surmount the antiarrhythmic effect of IVB inflation.

Methods Male Wistar rat (285–400 g) hearts were Langendorff-perfused with an IVB positioned in the left ventricle and minimally inflated (0.01 ml) to give a detectable developed pressure (~30 mmHg; 'IVB' groups) or inflated substantially (0.12 ml) to give a developed pressure >100 mmHg ('IVB inflated'). Baseline assessment (–11 min) during perfusion with Krebs' (modified to contain 4 mM K⁺) was followed by randomized and blinded switch to test solution at –10 min, then left coronary artery ligation at time zero, with ischaemia maintained for 60 min. Test solution comprised Krebs' containing catecholamines (93.9 nM noradrenaline and 22.5 nM adrenaline in 15 mM ascorbate vehicle) or vehicle alone (n=9/group). Design (blinded and randomized) and data analysis (e.g. use of ANOVA for Gaussian-distributed data and Fisher's exact test for VF incidence) accorded with BPS guidelines.³

Results Heart rate and developed pressure were increased by catecholamines (Cat) from 1 min before ligation (–1 min) (294 ± 6, 310 ± 13 to 437 ± 10, 442 ± 13 Beats/min and 28 ± 2, 101 ± 3 to 94 ± 14, 177 ± 10 mmHg for IVB and IVB inflated groups respectively), and the effect on pressure was exacerbated by IVB inflation (IVB 30 ± 3 mmHg vs IVB inflation 101 ± 3 mmHg). Ischaemia reduced developed pressure, with effects sustained during ischaemia. Mean ischaemic zone size varied between groups from 53 ± 2 to 59% ± 1% (p > 0.05). Cats increased VF incidence (Vehicle 0% vs Cats 56%) (p < 0.05) and extended the susceptibility time window past 30 min of ischaemia, but IVB inflation was antiarrhythmic during ischaemia and surmounted the arrhythmia facilitating effect of catecholamines (IVB inflated +CATs 0% vs IVB +Cats 56%).

Conclusion Catecholamine perfusion was unable to surmount IVB-induced VF suppression. Unfortunately this rendered VF incidence too low to permit the assay to be suitable for evaluating drug effects on VF and contractile function contiguously.

REFERENCES

1. Wilder CDE, et al. *Br J Pharmacol* 2016;**173**:39–52.
2. Wilder CDE, et al. 2016. <http://www.pa2online.org/abstracts/vol13issue3abst245p.pdf>
3. Curtis MJ, et al. *Br J Pharmacol* 2015;**172**:2671–2674.

6

ZINC ATTENUATES UVA-DEPENDENT LABILE IRON INCREASE IN HUMAN DERMAL FIBROBLASTS: IMPLICATIONS FOR SKIN AGEING

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Introduction To protect the cell from damaging oxidative stress induced by Fenton reactions, the cytosolic labile iron pool (LIP) is normally kept low and tightly regulated. These reactions are initiated by interactions between iron and hydrogen peroxide and can be prolonged and increased with ascorbate. The source of cytosolic labile iron is unclear. It has been suggested that lysosomes are the main source of iron, since protease inhibitors reduce leakage of lysosomal contents including iron after UVA (ultraviolet light) exposure. However, the time resolution of the changes in enzyme activity required to assess lysosomal leakage is too long to establish whether lysosomal damage occurs due to secondary response to iron release from other sources, particularly ferritin. Other methods are therefore required to clarify the source of cytosolic labile iron. Zinc is a redox-inert metal that has anti-oxidant, anti-inflammatory and anti-proliferative properties which is notably reduced in patients with subclinical carotid atherosclerosis, acute coronary syndrome and heart failure. Zinc is known to block iron diffusion via ferritin threefold channels and can therefore be used as a tool to examine UV-induced iron release from ferritin.

Methods A fluorescence probe (FeRhoNox-1) specific for ferrous ion was used to determine the time dependent changes in human fibroblasts following exposure to UVA irradiation. Since it is known that low concentrations of zinc block iron diffusion via ferritin threefold channels, we reasoned that pre-incubating skin cells with low concentrations of ZnCl₂ would inhibit iron release from ferritin after photo-activation by UVA. Confluent monolayers of human dermal fibroblasts were incubated overnight with 10 μM FeSO₄ and 0, 10 and 40 μM ZnCl₂, before being loaded with FeRhoNox-1 and exposed to UVA (360 nm) for 1–10 min (8–80 J/m²), with fluorescent readings gathered at 1 min intervals.

Results The control cell iron dependent fluorescent signal increased by approximately 100% after 10 min UVA irradiation compared to pre-UV baseline (p < 0.001). This UVA-dependent increase in cell iron is prevented by both 10 and 40 μM ZnCl₂.

Conclusions These Results suggest that UVA causes a significant increase in skin fibroblast LIP and hence oxidative stress which may exacerbate the ageing phenotype of dermal cells. This LIP is likely to be sourced mainly from ferritin since this is completely blocked by relatively low concentrations of extracellular ZnSO₄.

7

DIETARY SULFORAPHANE REDUCES PERI-INFARCT CONSTRICTION FREQUENCY IN MOUSE BRAIN FOLLOWING FOCAL CEREBRAL ISCHAEMIA VIA A NRF2-INDEPENDENT MECHANISM

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Introduction The dietary isothiocyanate sulforaphane (SFN) obtained from precursors in cruciferous vegetables such as broccoli is a potent inducer of endogenous antioxidant defences. As a strong electrophile, it oxidises cysteine residues in the redox sensor Keap1 inducing activity of the transcription factor Nrf2 and upregulation of target antioxidant and detoxifying genes. We have previously demonstrated that oral administration of doses achievable through diet for three days