PATHOLOGICAL RECLASSIFICATION OF BCC FROM THE ONTRAC SKIN CANCER CHEMOPREVENTION STUDY & 2018 WHO CLASSIFICATION OF SKIN TUMORS

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OUR NATIONAL CANCER

- BCCs are the most common malignant tumours in humans
- Australia has highest incidence of BCCs worldwide
- Cost to healthcare system of ~ $2459/case of KC (keratinocyte cancer)

Australian Institute of Health and Welfare, Estimated most common cancers diagnosed, 2018 MJA, 2012
SKIN CARCINOGENESIS

UV immunosuppression (↓ anti-tumour immune response) → DNA Damage → DNA Repair (X) → Mutations → Genomic Stability → Cancer
Additional preventative strategies urgently needed to reduce actinic cancer
ORAL NICOTINAMIDE TO REDUCE ACTINIC CANCER (ONTRAC)

A double-blind, multi-centre, phase 3, centrally randomised controlled trial
NICOTINAMIDE - MECHANISMS

- Amide form of vitamin B3
- Photoprotective in mice
- Precursor of NAD+ (cofactor in ATP production = ENERGY)

Gensler, 1997, 1999
By replenishing energy, nicotinamide enhances DNA repair

- Human keratinocytes
- Melanocytes
- Ex vivo skin
- Phase 2 study

UV immunosuppression (↓ anti-tumour immune response)
Phase 3 Study

386 patients (high risk)

1g nicotinamide (B3) daily vs placebo for 12 months

Primary endpoint:

New histologically confirmed KCs (BCC + SCC) at 12 months
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

**RATE OF KC 23% LOWER AT 12 MONTHS VS PLACEBO**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo mean no. of lesions/person</th>
<th>Nicotinamide</th>
<th>Rate Ratio (95% CI)</th>
<th>Relative Difference, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12-mo intervention period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSCs</td>
<td>2.4</td>
<td>1.8</td>
<td>23 (4 to 38)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>BCCs</td>
<td>1.7</td>
<td>1.3</td>
<td>20 (-6 to 39)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>SCCs</td>
<td>0.7</td>
<td>0.5</td>
<td>30 (0 to 51)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td><strong>6-mo postintervention period</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NMSCs</td>
<td>0.8</td>
<td>0.8</td>
<td>-17 (-59 to 14)</td>
<td>0.33</td>
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</tr>
<tr>
<td>BCCs</td>
<td>0.6</td>
<td>0.5</td>
<td>-6 (-53 to 26)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>SCCs</td>
<td>0.3</td>
<td>0.3</td>
<td>-59 (-163 to 4)</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

Negative binomial model; relative rates, relative rate reductions, and p-values from model with centre and 5y skin cancer history as covariates.
SIGNIFICANT REDUCTION IN AKs

Figure 3. Change from Baseline to Month 12 in Number of Actinic Keratoses.
CLASSIFICATION OF ONTRAC KCs

- All BCCs classified as high risk type reviewed (n= 139)
- National and international guidelines recommend more aggressive treatment for high risk subtypes
- All squamous carcinomas reviewed
~66 subtypes described in literature
Poor inter-observer variability
Definitions of high risk subtypes imprecise
More precise definitions for high risk subtypes & simplified two tier classification proposed by risk of recurrence
Basal cell carcinoma

Table 1.01 Histological subtypes of basal cell carcinoma (BCC) stratified by risk of recurrence

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular BCC</td>
<td>Basosquamous carcinoma *</td>
</tr>
<tr>
<td>Superficial BCC</td>
<td>Sclerosing/morpheic BCC *</td>
</tr>
<tr>
<td>Pigmented BCC</td>
<td>Infiltrating BCC</td>
</tr>
<tr>
<td>Infundibulocystic BCC</td>
<td>BCC with sarcomatoid differentiation *</td>
</tr>
<tr>
<td>(a variant of BCC with adnexal differentiation)</td>
<td>Micronodular BCC</td>
</tr>
<tr>
<td>Fibroepithelial BCC</td>
<td></td>
</tr>
</tbody>
</table>

* denotes special subtypes.
MICRONODULAR BCC

- Irregular, tentacular and infiltrative deep or peripheral edge
- Composed predominantly (>50%) of small discrete nodules < 0.15 mm in diameter
- Often extend deeply into or beyond the dermis
- Perineural invasion more common

Elder DA, Massi D, Scolyer RA, Wilemze E (Eds) Pathology and Genetics of Tumours of the Skin, World Health Organization Classification of Tumours, IARC, 5th edition, 2018
NOT MICRONODULAR!
INFILTRATING BCC

- Irregular/tentacular/infiltrative/permeating pattern of invasion
- Varially sized infiltrative jagged nests of basaloid tumour cells (~ 5–8 cells thick)
- Perineural invasion increased
- ~ ⅓ admixed with nodular BCC component
- Overlap with sclerosing/morphoeic BCC

Elder DA, Massi D, Scolyer RA, Wilemze E (Eds) Pathology and Genetics of Tumours of the Skin, World Health Organization Classification of Tumours, IARC, 5th edition, 2018
**MORPHOEIC (SCLEROSING) BCC**

- Irregular/tentacular, deeply infiltrative border
- Narrow cords of tumour (1–5 cells thick) compressed by induced sclerotic collagenous stroma
- Retraction artefacts uncommon
- Often overlap with infiltrating BCC, which lacks the prominent induced collagenous stroma

Elder DA, Massi D, Scolyer RA, Wilemze E (Eds) Pathology and Genetics of Tumours of the Skin, World Health Organization Classification of Tumours, IARC, 5th edition, 2018
Transplant recipients 80x risk SCC and 16x risk BCC

Well tolerated in phase 2 study

ONTRANS: multicentre phase 3 study in progress

2018 WHO criteria to be applied

FUTURE DIRECTIONS

- Chemoprevention in Melanomas
- Immunological mechanisms
- Inter observer reproducibility study using WHO criteria

Minocha et al., Journal of Investigative Dermatology, 2019
Thompson et al., Experimental Dermatology, 2014
Practice changing: chemoprevention for high risk patients

- Simplified 2 tier system and more precise criteria for classification of high risk BCC in WHO 4th edition
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