Future Therapeutic Developments in Head and Neck Cancer

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Predictions for Future Paradigm Shifts

- New radiation technologies (MR-Linac)
- Novel mechanism-based radiosensitisers
- Immunotherapies for H&N cancer.
Predictions for Future Paradigm Shifts

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Development and Optimization of MR-Guided RT

MR LINAC

- Accelerator
- Collimator
- Beam

MRI Scanner

Courtesy of B. Raaymakers (UMC)
MR-Linac Acquisition at The Royal Marsden/ICR

Membership of global consortium (n=7)

Business plan completed

Multi-tumour site focus (H&N important player)
In-Room MRI Guidance

Current In-Room CBCT

Future In-Room MRI

Exploitable Advantages:

• Enhanced soft tissue contrast of MRI
• Real-time imaging
• Real-time treatment adaptation
• No radiation dose and non-invasive
The Royal Marsden

Development of Accurate and Reliable Dosimetry

Challenges:

• Investigate detector responses
• Validate dose calculations of RT planning system by dosimetry
• Develop clinical dosimetry protocols

Impact of electron ‘bending’ on dosimetry
Development of Real-Time Adaptive Radiotherapy

Challenges:
- Optimise fast MR image acquisition
- Develop ultra-fast treatment plan re-optimisation
- Develop on-line treatment field adaptation using MLC
Q: Advantages of MR-Linac technology will include:

A. Reduced normal tissue toxicity
B. The ability to “see” the tumour at the same time as delivering radiation
C. The potential to increase the radiation dose to the tumour
D. All of the above
Predictions for Future Paradigm Shifts

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“Synthetic Lethality”
Targeting Intermediate/High-Risk Disease

- Aim is addition of targeted radiosensitiser to platin-based chemoradiation
Treatment Delivery According to Risk Group

- Studies in intermediate-/high-risk disease
- Studies in low-risk disease

Ang et al. NEJM 2010
Q: New radiosensitising drugs are likely to most applicable to patients with:

A. Early-stage head and neck cancers
B. Intermediate-stage head and neck cancers
C. Late-stage head and neck cancers
D. All of the above
Predictions for Future Paradigm Shifts

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Next Generation: Immune Checkpoint Blockade

Anti-PD1 MAB
Anti-PD-L1 MAB

Anti-CTLA4 MAB
The Royal Marsden

The Power of the New Immunotherapies

BRAF$^\text{wt}$

Biochemo

HD IL-2

Ipi

Baseline

Day 90

CD8$^+$

CD8$^+$

N ENGL J MED 369;2  NEJM.ORG  JULY 11, 2013
MK3475 (Pembrolizumab) in Melanoma

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ORR by RECIST, %</th>
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<tbody>
<tr>
<td></td>
<td>No previous ipilimumab</td>
</tr>
<tr>
<td>10 mg/kg Q2W (n = 52)</td>
<td>49</td>
</tr>
<tr>
<td>10 mg/kg Q3W (n = 45)</td>
<td>26</td>
</tr>
<tr>
<td>2 mg/kg Q3W (n = 20)</td>
<td>25</td>
</tr>
</tbody>
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Q3W, every 3 weeks.
KEYNOTE-012

56 pts R/M H&N Cancer → MK-3475 Single agent → Toxicity Response PFS OS

### Best Overall Response Rates in Advanced Head and Neck Cancer

<table>
<thead>
<tr>
<th>Patients Evaluable for Response</th>
<th>Total Head/neck N=56*</th>
<th>HPV Positive N=20</th>
<th>HPV Negative N=36***</th>
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<tbody>
<tr>
<td><strong>Response Evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>10 (18)</td>
<td>3 (15)</td>
<td>7 (19)</td>
</tr>
<tr>
<td><strong>Best Overall Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Complete + Partial)**</td>
<td>11 (20)</td>
<td>4 (20)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>16 (29)</td>
<td>8 (40)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>25 (45)</td>
<td>7 (35)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>No Assessment</td>
<td>4 (7)</td>
<td>1 (5)</td>
<td>3 (8.3)</td>
</tr>
</tbody>
</table>

*95% CI:
- Complete Response: 0.0, 9.6
- Partial Response: 8.9, 30.4
- Best Overall Response: 10.2, 32.4
- Stable Disease: 17.3, 42.2
- Progressive Disease: 31.3, 58.5
- No Assessment: 2.0, 17.3

Seiwert et al ASCO 2014
Systemic effects of local radiotherapy
Silvia C Formenti, Sandra Demaria

- Patient with thymic carcinoma
- 2 Lung lesions, one irradiated, one not irradiated
The Power of the New Immunotherapies

Abscopal response in irradiated lesion

Ab = away from Scopus = the target

Steps in Generating Immune Responses

Tesniere et al. Cell Death & Differentiation 2008
Potential Modulation of Immune Responses

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors
Radiation as a Form of Active Immunotherapy

- Increased expression of MHC-I
- Generation of novel peptides
- Increased CD8 T-cell recognition and lysis

Radiation

- Induction of apoptosis
  - Expression of calreticulin, phosphatidylserine
  - Release of endogenous danger signals e.g. HMGB1, HSP, uric acid

Engulfment by professional APC
- Maturation/activation
- Cross-presentation of tumour antigen

Irradiated tumour cell

- Increased expression of NKG2D ligands
- NK-cell recognition and lysis

NK

T-cell activation, tumour targeting and destruction; generation of protective immunity

DC

CD8 T-cells
Q: New immunotherapies are most likely to contribute to curing head and neck cancers as:

1 - Single-agent therapies

2 - Part of combination regimens with radiotherapy

3 - Part of combination regimens with surgery

4 - Part of combination regimens with chemotherapy
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