Chemotherapy
In
Head and Neck Cancer

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Introduction - Approach to Topic

- Importance of systemic treatment in cancer
- Need for systemic treatment in head neck cancer
- Methods for integration of systemic treatment with local treatment
- Evidence base for integration of treatment modalities
I Shall NOT Discuss..

- Newer agents for chemotherapy
- Chemo-radiotherapy
- Biological response modifiers
- Altered fractionation and chemotherapy
Importance of Systemic Treatment in Cancer
Importance of Systemic Treatment in Cancer

- Paul Ehrlich coined the term *chemotherapy*
- Wide usage in various hematological and solid malignancies with varied success
- Obstacles to efficacy: toxicity to the normal tissues and development of cellular drug resistance
Chemotherapy- Clinical Applications in solid tumours

- **Mainstay of treatment**

  For cancers which are curable by chemotherapy either alone or in combination with other modalities like Radiotherapy or surgery

  - Lymphoma
  - Paediatric malignancies
  - Choriocarcinoma
  - Testicular Tumours
Chemotherapy - Clinical Applications

- Neoadjuvant treatment
  - For patients with locally advanced disease for whom local forms of therapy, such as surgery or radiation, or both, are inadequate by themselves

- Anal cancer
- Bladder cancer
- Breast cancer
- Esophageal cancer
- Head and neck cancer
- Gastric cancer
- Osteogenic sarcoma
- Rectal cancer
- Soft tissue sarcoma
Chemotherapy- Clinical Applications

- Adjuvant treatment
  To treat micrometastatic disease at a time when tumor burden is at a minimum, thus enhancing the potential efficacy of drug treatment

- Breast cancer
- Colorectal cancer
- Gastric cancer
- Non–small cell lung cancer
- Osteogenic sarcoma
- STS of extremities
Clinical End Points in Evaluating Response to Chemotherapy

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Response Rates:</strong> Help in Prognostic stratification of patients Eg. Osteosarcoma</td>
<td></td>
</tr>
<tr>
<td>• <strong>Organ conservation rates:</strong> eg Larynx, breast etc</td>
<td></td>
</tr>
<tr>
<td>• <strong>Survival:</strong> doubtful</td>
<td>• <em>survival</em>: most important determinant</td>
</tr>
<tr>
<td></td>
<td>• <strong>Response Rates:</strong> cannot be used to measure efficacy as the primary tumour removed already</td>
</tr>
</tbody>
</table>
Mechanisms for Enhanced Efficacy by Addition of Chemotherapy

- Spatial Co-operation
- Independent toxicity
- Radiosensitization
- Protection of normal tissues

AIMED AT INCREASING THE THERAPEUTIC RATIO OF TREATMENT
Need for Systemic Treatment in Head Neck Cancer
Presentation of Head Neck Cancer

- Usual mode of presentation: advanced but regionally localized disease
- Advanced disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
<th>Survival (3 Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$T_3N_0M_0$ or $T_{1-3}N_1M_0$</td>
<td>50-75%</td>
</tr>
<tr>
<td>Poor</td>
<td>$T_4N_{0-1}M_0$ or $T_{1-4}N_{2-3}M_0$</td>
<td>20-45%</td>
</tr>
</tbody>
</table>
Need for Systemic Treatment in Head Neck Cancer

- <10% of patients with head neck cancer have metastatic disease at diagnosis

  But

- >50% of patients have micro metastasis at autopsy
Need for Systemic Treatment in Head Neck Cancer

• There has been remarkable improvement in local control in head neck cancer by the use of various techniques like
  – Altered fractionation
  – Concurrent chemo radiotherapy and
  – IMRT/3D-CRT

* This improvement in local control might make systemic disease burden an important determinant of survival in the future
Evolution of Chemotherapy In Head Neck Cancer

• Unusual sensitivity of Squamous cell cancer of head neck region to chemotherapy
• Initially used for metastatic/recurrent disease
• Use of single agent methotrexate/cisplatinum showed response rates of 30% in this situation
Evolution of Chemotherapy In Head Neck Cancer

• High response rates when used in previously untreated patients- Neoadjuvant setting

• Progression from single agent to multiagent chemotherapy showed improved response rates but no survival advantage
Combination Vs Single Agent Chemotherapy

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Methotrexate</th>
<th>Mtx+CDDP+Bleomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>ORR</td>
<td>35%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Survival Similar in both arms
Summary of Results of Phase II Trials of Neo-adjuvant Chemotherapy

- ORR 80-100%
- CR 20-50%
- CR correlates with good prognosis
- No value of >3 cycles of chemotherapy
- T & N stage & PS consistent prognostic factors
- Lack of response to chemotherapy predicts lack of response to Radiotherapy as well
- Local treatment not technically jeopardized
## Randomized Control Trials

**Phase III**

Single agent Methotrexate based

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of patients</th>
<th>Response rates</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowlton et al</td>
<td>96</td>
<td>NA</td>
<td>No diff in survival</td>
</tr>
<tr>
<td>Fazekas et al</td>
<td>638</td>
<td>NA</td>
<td>No diff in survival</td>
</tr>
<tr>
<td>Taylor et al</td>
<td>95</td>
<td>6% 34%</td>
<td>No diff in survival</td>
</tr>
</tbody>
</table>
## Non Platinum Multi-agent Chemotherapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Chemotherapy agents</th>
<th>Response rates</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stell et al</td>
<td>86</td>
<td>O,B,5fu,Mtx, Cort,6MP, Cy</td>
<td>NA, NA</td>
<td>No diff in surv.</td>
</tr>
<tr>
<td>Stolwijk et al</td>
<td>68</td>
<td>V,Mtx, Cyclo,5fu</td>
<td>NA, NA</td>
<td>No diff in surv.</td>
</tr>
<tr>
<td>Holoye et al</td>
<td>83</td>
<td>B,Cyclo,Mtx, 5fu</td>
<td>5%, 67%</td>
<td>No diff in surv.</td>
</tr>
</tbody>
</table>
Platinum Based Multi Agent Chemotherapy

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<th>Outcome</th>
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<tbody>
<tr>
<td>Toohill et al</td>
<td>60</td>
<td>Cisplatin+5FU</td>
<td>19% 67%</td>
<td>No diff in surv.</td>
</tr>
<tr>
<td>Martin et al</td>
<td>75</td>
<td>Cisplatin+5FU</td>
<td>46% 22%</td>
<td>No diff in surv.</td>
</tr>
</tbody>
</table>
Problems in Studies…

• Large number of trials using ineffective chemotherapy regimes
• Inadequate doses of drugs used in significant number of trials
• Intrinsic flaws in design of a number of trials
• A look at some of the better designed trials…
## Studies With Minimal Deficiencies

<table>
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<th>Authors</th>
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<th>Chemotherapy agents</th>
<th>Response rates</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuller et al</td>
<td>158</td>
<td>Cisplatin, Mtx, Bleomycin, Vincristin</td>
<td>19% 51%</td>
<td>Decreased distal Metastasis</td>
</tr>
<tr>
<td>H&amp;N Contracts Study</td>
<td>402</td>
<td>Cisplatin, Bleomycin, Mtx</td>
<td>3% 34%</td>
<td>Survival Benefit by subgroup analysis, Decreased distal Metastasis</td>
</tr>
</tbody>
</table>
## Organ Preservation

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Follow up</th>
<th>Results</th>
</tr>
</thead>
</table>
| Veterans Affairs Larynx Trial | PF, three cycles; radiotherapy     | 12 y      | • Larynx preserved in 60% of survivors  
• No difference in survival,  
• Reduced distal metastasis with PF |
| EORTC Hypopharynx         | PF, three cycles; radiotherapy     | 10 y      | • Larynx preserved in 30% of survivors,  
• Survival equivalent  
• Reduced distal metastasis |
## Survival Benefit

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<tr>
<th>Study</th>
<th>Treatment</th>
<th>Follow up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studio trial</td>
<td>PF four cycles; surgery and/or radiotherapy</td>
<td>10 y</td>
<td>Significant improvement in survival in unresectable patients; reduced distal metastasis</td>
</tr>
<tr>
<td>GETTEC Oropharynx trial</td>
<td>PF three cycles; surgery and/or radiotherapy</td>
<td>5y</td>
<td>Significant improvement in survival</td>
</tr>
</tbody>
</table>
Summary of Phase III Trials of Neo-adjuvant Therapy

• Cisplatin and 5 Fluorouracil induction chemotherapy best studied
• Larynx preservation possible in operable/resectable cases of carcinoma Hypopharynx and Larynx
• Survival benefit limited to subset of patients with unresectable disease
• In all other situations benefit is questionable
Large Number of Trials -
Large Number of Conflicting Results

Meta-Analysis
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>4292</td>
<td>7828</td>
<td>5079</td>
<td>10,741</td>
</tr>
<tr>
<td>Main endpoints</td>
<td>Survival, LC, Distal Mets</td>
<td>Survival, LC, Distal Mets</td>
<td>Survival, LC, Response at 2 Months</td>
<td>DFS</td>
</tr>
</tbody>
</table>
Summary of Results of Meta-analyses

• General class of induction trials did not improve survival compared to standard therapy
• Subset of induction chemotherapy trials using Cisplatin/5FU (PF) chemotherapy resulted in 5% improvement in 5 year survival
Summary of Results of Meta-analyses

• Difference less substantial than 8% improvement seen with concurrent chemotherapy trials

• Interpretation confounded by non PF regimes, ineffective PF regimes and carboplatin containing regimes - inferior to cisplatin in HNC
Adjuvant Treatment

• Traditional adjuvant treatment in HNC has been radiotherapy in situations where risk of disease recurrence above clavicles exceeds 20%

  ➢ Close/+ve margins
  ➢ Extent of nodal involvement
  ➢ Extra capsular spread
  ➢ Distribution of involved nodes at lower levels in neck
  ➢ PNI/LVI
Adjuvant Chemotherapy

• Till date adjuvant chemotherapy has been used only in advanced disease

• Evidence base for use is difficult to obtain as trials include heterogeneous patient populations and combinations of neo adjuvant, concurrent and adjuvant settings
### Adjuvant Chemotherapy Without Concurrent Radiotherapy RCT

Only post-operative chemotherapy

<table>
<thead>
<tr>
<th>Author/Group</th>
<th>Standard treatment</th>
<th>Experimental treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup 0034</td>
<td>RT</td>
<td>Cisplatin &amp; 5FU followed by RT</td>
<td>No difference in survival. Distant metastasis decreased for CT group</td>
</tr>
<tr>
<td>French</td>
<td>RT</td>
<td>RT followed by cisplatin, bleomycin and Mtx</td>
<td>Better Locoregional control for CT but worse OS</td>
</tr>
<tr>
<td>Japanese</td>
<td>Surgery or RT</td>
<td>Uracil &amp; Tegafur</td>
<td>For surgery patients only decreased distal metastasis, no change in OS</td>
</tr>
</tbody>
</table>
# Adjuvant Chemotherapy Without Concurrent Radiotherapy RCT

## Pre-operative and postoperative chemotherapy

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<tr>
<th>Author/Group</th>
<th>Standard treatment</th>
<th>Experimental treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contracts</td>
<td>Sx+ PORT</td>
<td>NACT(Cis+Bleo) followed by standard treatment NACT-Standard treatment- Adjuvant Cisplatin x 6 m</td>
<td>No difference in survival</td>
</tr>
<tr>
<td>Ervin</td>
<td>Neo-adjuvant CT(P+Bl+Mtx +Lv)</td>
<td>Maintenance in responders with same regime x 3 cycles</td>
<td>3 yr DFS improved for maintenance Ct</td>
</tr>
<tr>
<td>Taylor</td>
<td>Local Therapy (Surgery + RT)</td>
<td>NACT( Mtx+Lv)- Local Therapy - CT</td>
<td>No difference in DFS and OS</td>
</tr>
<tr>
<td>Rentschler</td>
<td>Surgery + RT</td>
<td>Escalating dose Mtx-Sx-Escalating dose Mtx-RT-Escalating dose Mtx</td>
<td>No difference in DFS and OS</td>
</tr>
</tbody>
</table>
Post-operative Adjuvant Chemotherapy With Concurrent Radiotherapy - RCT

- Used primarily with the intention of enhancing the efficacy of radiotherapy in high risk patients
- Cisplatin added mainly as a radiosensitizer
- Mitomycin used primarily as a hypoxic cytotoxic
## Post-operative Adjuvant Chemotherapy With Concurrent Radiotherapy - RCT

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<th>Experimental treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachaud</td>
<td>RT</td>
<td>CT-RT (Cisplatin)</td>
<td>Median survival and 5 Yr survival superior for CT-RT</td>
</tr>
<tr>
<td>Haffty</td>
<td>RT</td>
<td>CT-RT (Mitomycin)</td>
<td>Decreased LR in CT-RT; No change in OS</td>
</tr>
<tr>
<td>Weissberg</td>
<td>RT</td>
<td>CT-RT (Mitomycin)</td>
<td>Trend to improvement in DFS for CRT; Better Local control</td>
</tr>
<tr>
<td>Weissler</td>
<td>RT twice daily</td>
<td>RT twice daily + cisplatin and 5FU</td>
<td>No difference in DFS or OS</td>
</tr>
</tbody>
</table>
Adjuvant Chemotherapy for Nasopharyngeal Carcinoma

• Most chemo & Radiosensitive entity of all HNC
• High incidence of distal metastasis cf other HNC
• Integration of chemotherapy into Radiotherapy has resulted in improved disease outcomes
RTOG 88-17 / Intergroup 0099: 1998

- RT alone vs RT with concurrent cisplatin chemotherapy and adjuvant cisplatin + 5-Fu In Stage III and IV disease
- Dose: 70 Gy to primary. For neck, 50 Gy for N0 disease, 66 Gy for nodes ≤ 2 cm, and 70 Gy for nodes > 2 cm
- Cisplatin given every 3 weeks at 100 mg/m² x 3 cycles. Then adjuvant chemo 4 weeks after finishing RT: cisplatin 80 mg/m² and 5-FU 1000 mg/m²/d by 96-hr infusion q4months x 3 cycles
RTOG 88-17 / Intergroup 0099: 1998

- Partial or radical neck dissections for persistent neck disease
- Median follow-up 2.7 years
- 3-year PFS 69% (RT+chemo) vs 24%.
- 3-year OS 78% vs 47%

First randomized trial to show a survival benefit for the use of concurrent chemotherapy in HNC

Adjuvant chemotherapy after concurrent CT-RT now standard of care in Nasopharyngeal cancer
Summary- Integration of Chemotherapy With Local Treatment in Head Neck Cancer
Neoadjuvant Chemotherapy

- Advantages
  - Least toxic
  - Maximize systemic therapy
  - Smaller area of local treatment if induction therapy shrinks tumor

- Disadvantages
  - Increased treatment time
  - Lack of local synergy
Concurrent Chemotherapy

• Advantages
  – Shorter treatment time
  – Radio sensitization

• Disadvantages
  – Compromised systemic therapy
  – Increased toxicity
  – No cytoreduction in tumor
Concurrent Followed by Adjuvant

• Advantages
  – Maximizes systemic therapy
  – Radiation enhancement
  – Local & distant therapy delivered upfront

• Disadvantages
  – Increased toxicity
  – Increased treatment time
  – Difficult to complete chemotherapy after ct-rt
Neoadjuvant Followed by Concurrent

- Advantages
  - Maximizes systemic therapy
  - Radiation enhancement

- Disadvantages
  - Increased toxicity
  - Increased treatment time
  - Difficult to complete ct-rt after chemotherapy
Questions Please…