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

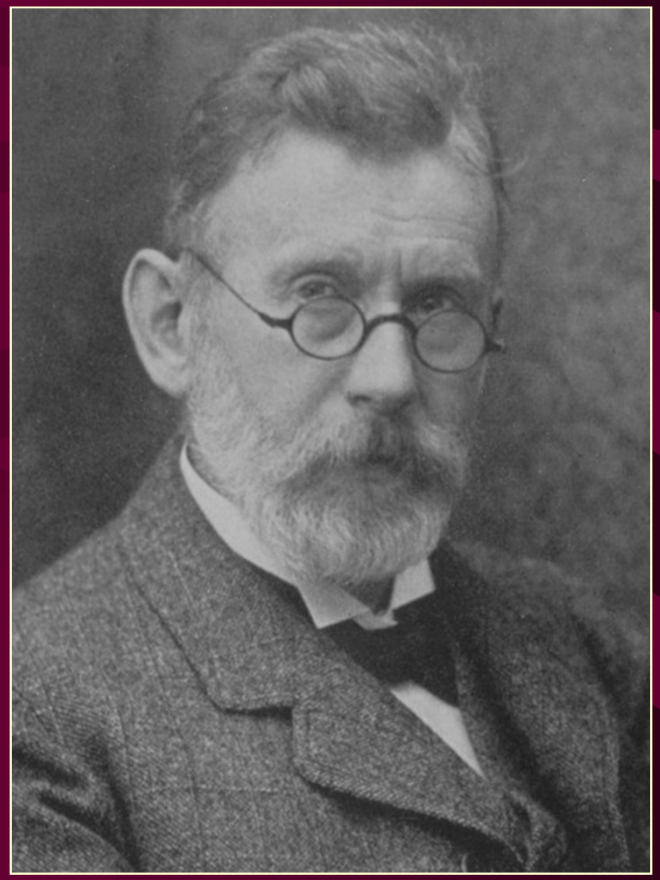
I Shall NOT Discuss..

- 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

Neoadjuvant	Adjuvant
•**Response Rates:** Help in Prognostic stratification of patients Eg. Osteosarcoma • **Organ conservation rates**: eg Larynx,breast etc • **Survival**: doubtful	• **survival :most important determinant** • **Response Rates:** cannot be used to measure efficacy as the primary tumour removed already

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

Category	Descriptor	Survival (3 Year)
Intermediate	$T_3N_0M_0$ or $T_{1-3}N_1M_0$	50-75%
Poor	$T_4N_{0-1}M_0$ or $T_{1-4}N_{2-3}M_0$	20-45%

Need for Systemic Treatment in Head Neck Cancer

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

But

- **>50% of patients 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 reponse 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

ECOG	Methotrexate	Mtx+CDDP+Bleomycin
CR	8%	16%
ORR	35%	48%
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

Authors	No of patients	Response rates		Outcome
		CR	PR	
Knowlton et al	96	NA	NA	No diff in survival
Fazekas et al	638	NA	NA	No diff in survival
Taylor et al	95	6%	34%	No diff in survival

Non Platinum Multi-agent Chemotherapy

Authors	Patients	Chemotherapy agents	Response rates		Outcome
			CR	PR	
Stell et al	86	O,B,5fu,Mtx, Cort,6MP, Cy	NA	NA	No diff in surv.
Stolwijk et al	68	V,Mtx, Cyclo,5fu	NA	NA	No diff in surv.
Holoye et al	83	B,Cyclo,Mtx, 5fu	5%	67%	No diff in surv.

Platinum Based Multi Agent Chemotherapy

Authors	Patients	Chemotherapy agents	Response rates		Outcome
			CR	PR	
Toohill et al	60	Cisplatin+5FU	19%	67%	No diff in surv.
Martin et al	75	Cisplatin+5FU	46%	22%	No diff in surv.

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

Authors	Patients	Chemotherapy agents	Response rates		Outcome
			CR	PR	
Schuller et al	158	Cisplatin, Mtx, Bleomycin, Vincristin	19%	51%	Decreased distal Metastasis
H&N Contracts Study	402	Cisplatin, Bleomycin, Mtx	3%	34%	Survival Benefit by subgroup analysis, Decreased distal Metastasis

Organ Preservation

Study	Treatment	Follow up	Results
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

Study	Treatment	Follow up	Results
Studio trial	PF four cycles; surgery and/or radiotherapy	10 y	Significant improvement in survival in unresectable patients; reduced distal metastasis
GETTEC Oropharynx trial	PF three cycles; surgery and/or radiotherapy	5y	Significant improvement in survival

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

	Stell 1992	Munro 1995	El Sayed 1996	MACH-NC 1998
No of Trials Included	28	54	42	63
Patients	4292	7828	5079	10,741
Period considered	Before 1991	1963-1993	1963-1993	1965-1993
Main end-points	Survival, LC, Distal Mets	Survival, LC, Distal Mets	Survival, LC, Response at 2 Months	DFS

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

Author/Group	Standard treatment	Experimental treatment	Outcome
Intergroup 0034	RT	Cisplatin & 5FU followed by RT	No difference in survival Distant metastasis decreased for CT group
French	RT	RT followed by cisplatin, bleomycin and Mtx	Better Locoregional control for CT but worse OS
Japanese	Surgery or RT	Uracil & Tegafur	For surgery patients only decreased distal metastasis, no change in OS

Adjuvant Chemotherapy Without Concurrent Radiotherapy RCT

Pre-operative and postoperative chemotherapy

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

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

Author/ Group	Standard treatment	Experimental treatment	Outcome
Bachaud	RT	CT-RT (Cisplatin)	Median survival and 5 Yr survival superior for CT-RT
Haffty	RT	CT-RT (Mitomycin)	Decreased LR in CT-RT; No change in OS
Weissberg	RT	CT-RT (Mitomycin)	Trend to improvement in DFS for CRT; Better Local control
Weissler	RT twice daily	RT twice daily + cisplatin and 5FU	No difference in DFS or OS

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 chemotherpay 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/m^2 x 3 cycles. Then adjuvant chemo 4 weeks after finishing RT: cisplatin 80 $mg/m^2$and 5-FU 1000 mg/m^2/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…