Nasopharyngeal Cancer/Multimodality Treatment

PANAGIOTIS KATSAOUNIS
Medical Oncologist
IASO GENERAL HOSPITAL
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INTRODUCTION

• The incidence of nasopharyngeal carcinoma demonstrates a marked geographical variation
• It is rare in the United States and Western Europe, with an incidence of 0.5 to 2 per 100,000
• It is endemic in southern China, including Hong Kong, where the incidence may reach 25 cases per 100,000 per year
• Populations that migrate from areas of high to low risk retain an elevated risk
• The incidence of nasopharyngeal carcinoma is two- to threefold higher in males compared with females
ETIOLOGY

• Diet (salted food, chinese herbs)
• Human papillomavirus (HPV) has been detected in a small subset of nasopharyngeal carcinoma patients in nonendemic, low-incidence regions among white individuals
• Heredity (1st degree relatives 7fold risk)
• Smoking
ETIOLOGY

• EBV is a primary etiologic agent in the pathogenesis of nasopharyngeal carcinoma

• Detection of both EBV deoxyribonucleic acid (DNA) and EBV gene expression in precursor lesions and tumor cells

• Nasopharyngeal carcinoma cells express a specific subgroup of EBV-latent proteins, including EBNA-1 and two integral membrane proteins, LMP-1 and LMP-2

• Latent membrane protein 1 (LMP1) is the major oncogene of EBV
Plasma EBV DNA level taken 6-8 weeks post RT: OS analysis using cutoff 500 copies/ml

P < 0.0001
Overall Survival By Post-RT EBV DNA Level

Lin JC et al, NEJM 2004

Le Q et al, CCR 2005
PATHOLOGY

- Nasopharyngeal carcinoma arises from the epithelial lining of the nasopharynx (WHO CLASSIFICATION)

  1) Keratinizing squamous cell carcinoma: The sporadic form (WHO type I)

  2) Nonkeratinizing carcinoma: differentiated (WHO type II)

  3) Nonkeratinizing undifferentiated (WHO type III) (strongly associated with Epstein-Barr virus (EBV))

  4) Basaloid squamous cell carcinoma (few reported cases, aggressive clinical course and poor survival)
### Primary tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor with parapharyngeal extension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor involves bony structures of skull base and/or paranasal sinuses</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space</td>
</tr>
</tbody>
</table>

### Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node(s) &gt; 6 cm and/or supraclavicular fossa</td>
</tr>
<tr>
<td>N3a</td>
<td>Greater than 6 cm in dimension</td>
</tr>
<tr>
<td>N3b</td>
<td>Extension to the supraclavicular fossa</td>
</tr>
</tbody>
</table>

### Distant metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Anatomic stage/prognostic groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
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</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage II</td>
<td>T1</td>
<td>N1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1</td>
<td>N2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T1</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T1</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>T1</td>
<td>T4</td>
<td>N3</td>
<td>M0</td>
</tr>
</tbody>
</table>

**NOTE:** cTNM is the clinical classification, pTNM is the pathologic classification.

* Parapharyngeal extension denotes posterolateral infiltration of tumor.
* The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.
* The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.
* Midline nodes are considered ipsilateral nodes.
* Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the thorax (Figure 4.2). Note that this would include caudal portions of levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.*
## Survival rates for nasopharyngeal cancer in an endemic population

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percent of patients</th>
<th>Five-year OS, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>90</td>
</tr>
<tr>
<td>II</td>
<td>41</td>
<td>84</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>IVA-B</td>
<td>28</td>
<td>58</td>
</tr>
</tbody>
</table>

OS: overall survival.

**TREATMENT** (EARLY STAGE I CANCERS)

- Early (stage I) cancers are treated with radiation therapy (RT) alone
- Good locoregional control
- Five-year overall survival rates of 90 percent for stage
- Outcomes have improved due to advances in RT planning and delivery
- With the use of magnetic resonance imaging (MRI), better staging
Concurrent Chemoradiotherapy vs Radiotherapy Alone in Stage II Nasopharyngeal Carcinoma: Phase III Randomized Trial

Qiu-Yan Chen, Yue-Feng Wen, Ling Guo, Huai Liu, Pei-Yu Huang, Hao-Yuan Mo, Ning-Wei Li, Yan-Qun Xiang, Dong-Hua Luo, Fang Qiu, Rui Sun, Man-Quan Deng, Ming-Yuan Chen, Yi-Jun Hua, Xiang Guo, Ka-Jia Cao, Ming-Huang Hong, Chao-Nan Qian, Hai-Qiang Mai

Manuscript received April 25, 2011; revised September 15, 2011; accepted September 27, 2011.
TREATMENT (INTERMEDIATE (STAGE II) DISEASE

Assessed for eligibility (n = 236)
- Excluded (n = 6)
  - Not meeting inclusion criteria (n = 2)
  - Refused to participate (n = 4)
  - Other reasons (n = 0)

Patients randomly assigned (n = 230)

CCRT arm
- Allocated to intervention (n = 116)
  - Received allocated intervention (n = 112)
  - Did not receive allocated intervention (n = 4)
- Lost to follow-up (n = 1)
  - Discontinued intervention (n = 0)
- Analyzed (n = 116)
  - Excluded from analysis (n = 0)

RT alone arm
- Allocated to intervention (n = 114)
  - Received allocated intervention (n = 114)
  - Did not receive allocated intervention (n = 0)
- Lost to follow-up (n = 0)
  - Discontinued intervention (n = 0)
- Analyzed (n = 114)
  - Excluded from analysis (n = 0)
TREATMENT (INTERMEDIATE (STAGE II) DISEASE

Figure 2. Kaplan-Meier estimates of patients who were randomly assigned to RT vs CCRT. A) Overall survival. Hazard ratio (HR) for overall survival favored CCRT (HR = 0.30, 95% CI = 0.12 to 0.76, P = .007, two-sided log-rank test). B) Progression-free survival (HR of progression = 0.45, 95% CI = 0.23 to 0.88; P = .017, two-sided log-rank test). CCRT = concurrent chemoradiotherapy; CI = confidence interval; HR = hazard ratio; RT = radiotherapy.
TREATMENT (INTERMEDIATE (STAGE II) DISEASE

• overall survival was significantly improved by the addition of concurrent cisplatin

• survival rate of 94.5 versus 85.8 percent, hazard ratio [HR] 0.30, 95% CI 0.12-0.76)

• improvement in distant metastasis-free survival (94.8 versus 83.9 percent)

• No difference in locoregional control (93.0 versus 91.1 percent)

• statistically significant increase in severe (grade 3 or 4) leukopenia/neutropenia, nausea/vomiting, and mucositis
Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099.

M Al-Sarraf, M LeBlanc, P G Giri, K K Fu, J Cooper, T Vuong, A A Forastiere, G Adams, W A Sakr, D E Schuller and J F Ensley
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE

• 193 patients registered, 147 (69 radiotherapy and 78 chemoradiotherapy)

• 3-year PFS rate was 24% versus 69%, respectively (P<.001)

• 3-year survival rate was 47% versus 78%, respectively (P = .005)

• **chemoradiotherapy is superior to radiotherapy** alone for patients with advanced nasopharyngeal cancers with respect to PFS and overall survival
Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis

Pierre Blanchard, MD, Prof Anne Lee, MD, Sophie Marguet, MSc, Julie Leclercq, MSc, Wai Tong Ng, MD, Prof Jun Ma, MD, Prof Anthony T C Chan, MD, Pei-Yu Huang, MD, Ellen Benhamou, MD, Guopei Zhu, MD, Daniel T T Chua, MD, Yong Chen, MD, Hai-Qiang Mai, MD, Dora L W Kwong, MD, Shie Lee Cheah, MD, James Moon, MSc, Yuk Tung, MD, Kwan-Hwa Chi, MD, Prof George Fountzilas, MD, Prof Li Zhang, MD, Edwin Pun Hui, MD, Prof Tai-Xiang Lu, MD, Prof Jean Bourhis, MD, Dr Jean Pierre Pignon, MD†† on behalf of the MAC-NPC Collaborative Group†

† Listed in the appendix
Published: 06 May 2015
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE

• data from 19 trials and 4806 patients
• median follow-up was 7.7 years (IQR 6.2-11.9)
• significantly improved overall survival (hazard ratio [HR] 0.79, 95% CI 0.73-0.86, p<0.0001
• absolute benefit at 5 years 6.3%, 95% CI 3.5-9.1)
Is CRT+A superior to CRT alone?

- No statistically significant difference between groups of trial
- Tendancy toward a stronger treatment effect with CRT+A
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE ADJUVANT

Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial

Lei Chen, MD†, Prof Chao-Su Hu, MD†, Prof Xiao-Zhong Chen, MD†, Prof Guo-Qing Hu, MD, Prof Zhi-Bin Cheng, MD, Prof Yan Sun, MD, Prof Wei-Xiong Li, MD, Yuan-Yuan Chen, MD, Fang-Yun Xie, MD, Shao-Bo Liang, MD, Yong Chen, MD, Ting-Ting Xu, MD, Bin Li, MD, Guo-Xian Long, MD, Si-Yang Wang, MD, Bao-Min Zheng, MD, Ying Guo, PhD, Ying Sun, MD, Yan-Ping Mao, MD, Ling-Long Tang, MD, Prof Yu-Ming Chen, PhD, Prof Meng-Zhong Liu, MD, Prof Jun Ma, MD

† Contributed equally to this study
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE ADJUVANT

• open-label phase 3 multicentre randomised controlled trial at seven institutions in China

• 251 patients in both groups received 40 mg/m² cisplatin weekly up to 7 weeks, concurrently with radiotherapy

• the concurrent chemoradiotherapy plus adjuvant chemotherapy group subsequently received 80 mg/m² adjuvant cisplatin and 800 mg/m² per day fluorouracil for 120 h every 4 weeks for three cycles
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE ADJUVANT

• RESULTS:

• median follow-up of 37·8 months (range 1·3–61·0)

• estimated 2 year failure-free survival rate was 86% (95% CI 81–90) in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 84% (78–88) in concurrent chemoradiotherapy only group (hazard ratio 0·74, 95% CI 0·49–1·10; p=0·13)
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE ADJUVANT

Randomized Trial of Radiotherapy Plus Concurrent–Adjuvant Chemotherapy vs Radiotherapy Alone for Regionally Advanced Nasopharyngeal Carcinoma


+ Author Affiliations
CONSORT flow diagram showing design, enrollment, and outcomes of this study (NPC-9901 Trial).

348 patients with T1-4 N2-3 M0 non-keratinizing nasopharyngeal carcinoma

Stratified by center, T and N category

Randomized

172 radiotherapy
Concurrent cisplatin + adjuvant cisplatin-fluorouracil

176 radiotherapy alone

2 did not receive chemotherapy

2 received chemotherapy

No of analyzed patients:
(Complete follow-up)
Outcome at last assessment
Alive:
  Relapse-free:
  Relapse salvaged:
  Relapse with disease:
Died:
  Disease progression:
  Treatment toxicity:
  Incidental cause:
  Unknown cause:

<table>
<thead>
<tr>
<th></th>
<th>172</th>
<th>165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>169</td>
<td>159</td>
</tr>
<tr>
<td>Relapse-free</td>
<td>101</td>
<td>85</td>
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<tr>
<td>Relapse salvaged</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Relapse with disease</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Died</td>
<td>63</td>
<td>78</td>
</tr>
<tr>
<td>Disease progression</td>
<td>42</td>
<td>66</td>
</tr>
<tr>
<td>Treatment toxicity</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Incidental cause</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Anne W. M. Lee et al. JNCI J Natl Cancer Inst
2010;102:1188-1198

© The Author 2010. Published by Oxford University Press.
Kaplan–Meier estimates of patients who were randomly assigned to radiotherapy (RT) vs chemoradiotherapy (CRT).
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE ADJUVANT

• 5-year progression-free survival (CRT vs RT: 62% vs 53%; P = .035)

• Deaths because of disease progression were reduced statistically significantly by 14% (CRT vs RT: 38% vs 24%; P = .008)

• BUT... 5-year overall survival was similar (CRT vs RT: 68% vs 64%; P = .22; hazard ratio of CRT = 0.81, 95% confidence interval = 0.58 to 1.13)

• deaths due to toxicity or incidental causes increased by 7% (CRT vs RT: 1.7% vs 0, and 8.1% vs 3.4%, respectively; P = .015)
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE ADJUVANT

• substantial differences exist in patient populations and trial designs
• preclude a definitive conclusion
• Toxicities should be taken into account
• New clinical trials needed to identify the optimal approach
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE (INDUCTION)

Docetaxel, cisplatin and 5-fluorouracil-based induction chemotherapy followed by intensity-modulated radiotherapy concurrent with cisplatin in locally advanced EBV-related nasopharyngeal cancer

P. Bossi¹, E. Orlandi², C. Bergamini¹, L. D. Locati¹, R. Granata¹, A. Mirabile¹, D. Parolini¹, M. Franceschini², C. Fallai², P. Olmi², P. Quattrone³, P. Potepan⁴, A. Gioghinì⁵, R. Miceli⁶, F. Mattana⁶, G. Scaramellini⁷ & L. Licitra¹*

¹Department of Medical Oncology; ²Department of Radiotherapy; ³Pathologic Unit; ⁴Department of Radiology; ⁵Department of Molecular Biology; ⁶Statistics Unit; ⁷Department of Otorhinolaryngology, Tumor National Institute, Milan, Italy

Received 4 November 2010; accepted 22 December 2010
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE (INDUCTION)

• 47 patients received induction chemotherapy of two to three cycles every 21 days with docetaxel 75 mg/m2 i.v., cisplatin 75 mg/m2 i.v. on day 1 and 5-FU 750 mg/m2/day by continuous infusion for 96 h.
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE (INDUCTION)

Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial

Prof Ying Sun, MD, Wen-Fei Li, MD, Prof Nian-Yong Chen, MD, Prof Ning Zhang, MD, Prof Guo-Qing Hu, MD, Prof Fang-Yun Xie, MD, Prof Yan Sun, MD, Prof Xiao-Zhong Chen, MD, Prof Jin-Gao Li, MD, Prof Xiao-Dong Zhu, MD, Prof Chao-Su Hu, MD, Prof Xiang-Ying Xu, MD, Yuan-Yuan Chen, MD, Prof Wei-Han Hu, MD, Prof Ling Guo, MD, Prof Hao-Yuan Mo, MD, Lei Chen, MD, Yan-Ping Mao, MD, Rui Sun, MD, Ping Ai, MD, Shao-Bo Liang, MD, Guo-Xian Long, MD, Bao-Min Zheng, MD, Xing-Lai Feng, MD, Xiao-Chang Gong, MD, Ling Li, MD, Chun-Ying Shen, MD, Jian-Yu Xu, MD, Ying Guo, PhD, Prof Yu-Ming Chen, PhD, Fan Zhang, MD, Li Lin, MD, Ling-Long Tang, MD, Prof Meng-Zhong Liu, MD, Dr Prof Jun Ma, MD

† Contributed equally to this study

Published: 26 September 2016
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE (INDUCTION)

- open-label, phase 3, multicentre, randomised controlled trial at ten institutions in China
- previously untreated, stage III–IVB (except T3-4N0) nasopharyngeal carcinoma
- concurrent chemoradiotherapy or concurrent chemoradiotherapy alone (three cycles of 100 mg/m² cisplatin every 3 weeks, concurrently with intensity-modulated radiotherapy)
- induction chemotherapy was three cycles of intravenous docetaxel (60 mg/m² on day 1), intravenous cisplatin (60 mg/m² on day 1), and continuous intravenous fluorouracil (600 mg/m² per day from day 1 to day 5) every 3 weeks
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE (INDUCTION)

- 3-year failure-free survival was 80% (95% CI 75–85) in the induction chemotherapy plus concurrent chemoradiotherapy group and 72% (66–78) in the concurrent chemoradiotherapy alone group (hazard ratio 0.68, 95% CI 0.48–0.97; p=0.034)
- Acceptable toxicity
- Follow-up is ongoing
TREATMENT/ADVANCED (STAGE III, IVA, AND IVB) DISEASE
TREATMENT-RELATED ACUTE COMPLICATIONS

• Mucositis is the predominant acute toxicity associated with radiation therapy
• Chemotherapy exacerbates mucositis
• Increased risks of neuropathy, emesis, neutropenia
• Nephrotoxicity
• Ototoxicity
TREATMENT-RELATED LATE COMPLICATIONS

• Lhermitte's Syndrome is common after chemoradiation (reversible demyelination of ascending sensory neurons)
• Xerostomia can be a long lasting or permanent problem
• Measurable deficits in cognitive function (short-term memory, language abilities) (Temporal lobes irradiation)
• Delayed bulbar palsy, developing 1 to 18 years post radiation, is reported in up to 20 percent of cases (CN IX,X,XI,XII) (dysphagia, dysarthria, nasal regurgitation)
• Hypothyroidism
• Skull base osteoradionecrosis with bleeding from the internal carotid artery
• Second neoplasms
TREATMENT  RECURRENT/METASTATIC DISEASE /SALVAGE SURGERY

• For carefully selected patients with local recurrence or an isolated relapse in the neck
• If small local recurrences and no distant metastases, nasopharyngectomy is an option
• Technically challenging
• Preserving neuromuscular bundle and critical mucosal barriers
• Role of endoscopic nasopharyngectomy?
TREATMENT   RECURRENT/METASTATIC DISEASE /SALVAGE SURGERY

• Three-year survival rates as high as 60 percent after salvage surgery have been reported for carefully selected patients

• Survival benefit may be restricted to those with T1 or T2 recurrent disease

• Serious surgical complications: 1) meningitis (the most common cause of perioperative mortality) 2) necrosis of the free flap 3) aspiration pneumonia
TREATMENT  RECURRENT/METASTATIC DISEASE/REIRRADIATION

• The potential for long-term survival with reirradiation has been demonstrated for subsets of carefully selected patients

• Reirradiation poses a therapeutic challenge since the dose that can be delivered safely is limited by previous RT treatments

• Significant acute and late toxicities must be expected

• Various treatment modalities (3D, IMRT,Stereotactic Radiotherapy, Proton Beam therapy, brachytherapy
TREATMENT RECURRENT/METASTATIC DISEASE/CHEMOTHERAPY

• Nasopharyngeal carcinoma is a highly chemosensitive tumor
• Reported response rates as high as 80 percent with some cisplatin-based regimens
• Platinum-containing doublet chemotherapy regimens preferred regimens
Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial

Prof Li Zhang, MD, Yan Huang, MD, Shaodong Hong, MD, Yunpeng Yang, MD, Gengsheng Yu, MD, Jun Jia, MD, Peijian Peng, MD, Xuan Wu, MD, Prof Qing Lin, MD, Prof Xuping Xi, MD, Jiewen Peng, MD, Mingjun Xu, MD, Prof Dongping Chen, MD, Xiaojun Lu, MD, Rensheng Wang, MD, Xiaolong Cao, MD, Xiaozhong Chen, MD, Prof Zhixiong Lin, MD, Jianping Xiong, MD, Qin Lin, MD, Conghua Xie, MD, Zhihua Li, MD, Prof Jianji Pan, MD, Jingao Li, MD, Prof Shixiu Wu, MD, Yingni Lian, MD, Quanie Yang, MD, Prof Chong Zhao, MD

† Contributed equally
TREATMENT RECURRENT/METASTATIC DISEASE/CHEMOTHERAPY

• 362 patients with recurrent or metastatic nasopharyngeal carcinoma from 22 hospitals in China were randomized in this multicenter, randomised, open-label, phase 3 trial.

• The median progression-free survival was 7·0 months (4·4–10·9) in the gemcitabine group and 5·6 months (3·0–7·0) in the fluorouracil group (hazard ratio [HR] 0·55 [95% CI 0·44–0·68]; p<0·0001).

• Serious treatment-related adverse events occurred in seven (4%) patients in the gemcitabine group and ten (6%) in the fluorouracil group.
Epidermal growth factor receptor

- 80% NPC overexpress EGFR
- LMP-1 induce EGFR upregulation
- EGFR gene amplification is common
- Negative prognostic factor

**Overall survival, Ma et al 2003**


Multicenter, Phase II Study of Cetuximab in Combination With Carboplatin in Patients With Recurrent or Metastatic Nasopharyngeal Carcinoma

Anthony T.C. Chan, Mow-Ming Hsu, Boon C. Goh, Edwin P. Hui, Tsang-Wu Liu, Michael J. Millward, Ruey-Long Hong, Jacqueline Whang-Peng, Brigette B.Y. Ma, Ka F. To, Matthias Mueser, Nadia Amellal, Xiao Lin, and Alex Y. Chang
TREATMENT RECURRENT/METASTATIC DISEASE

• Phase II study, 60 patients with epidermal growth factor receptor—expressing NPC who progressed on or within 12 months after termination of platinum-based chemotherapy for recurrent or metastatic disease

• Of the 59 patients assessable for efficacy, there were seven partial responses (11.7%), 29 patients (48.3%) with stable disease, and 23 patients (38.3%) with progressive disease, giving an overall response rate of 11.7% (95% CI, 4.8% to 22.6%)

• Results with EGFR tyrosine kinase inhibitors (gefitinib, erlotinib) have been disappointing
TREATMENT RECURRENT/METASTATIC DISEASE

• Vascular endothelial growth factor inhibition
• Small clinical trials with TKI inhibitors
• Sorafenib, sunitib, pazopanib and axitinib have shown activity
• Larger prospective clinical trials required to confirm this activity
ECC 2015: Pembrolizumab in Patients With Advanced Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Trial

By The ASCO Post
Posted: 10/2/2015 12:32:23 PM
Last Updated: 10/2/2015 12:32:23 PM

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A phase I study with anti-PD-1 agent pembrolizumab in heavily pretreated patients with advanced nasopharyngeal cancer demonstrated an overall response rate of 22.2%. Additionally, 55.6% of patients had stable disease (n = 15/27; 95% CI, 35.3–74.5); the disease control rate was 77.8% (n = 21/27; 95% CI, 57.7–91.4); and tumor shrinkage was achieved in 67% of patients. The median response duration was 10.8 months (range, 4.8–10.8). Phase II studies with nivolumab and pembrolizumab are ongoing.
FUTURE PERSPECTIVES

NRG-HN001 protocol study schema

Pre-RT
- Stage II-IVB NPC
- Detectable plasma EBV DNA
- To receive: Weekly cisplatin 40mg/m² and concurrent IMRT over 33 days

Post-RT
- High risk: Detectable plasma EBV DNA
- Low risk: Undetectable plasma EBV DNA

Randomise
- Stratify by T, N and Zubrod PS

Arm 1: Control arm. Adjuvant Cisplatin-5FU every 28 days for 3 cycles
Arm 2: Experimental arm: Adjuvant Gemcitabine-paclitaxel every 21 days for 4 cycles.
Arm 1: Control arm. Adjuvant Cisplatin-5FU every 28 days for 3 cycles
Arm 2: Experimental arm: Observation

Courtesy Dr. QT Le
FUTURE PERSPECTIVES

Efficacy of recombinant Epstein-Barr virus (EBV) vaccine in patients with NPC who had residual EBV DNA load after conventional therapy
ClinicalTrials.gov Identifier: NCT01094405

Primary endpoint
- Clinical benefit rate (CBR, percent of patients experiencing CR, PR or SD for at least 12 weeks from post cycle 2 to cycle 6 measurements) determined according to the Response Evaluation Criteria in Solid Tumours (RECIST)

Treatment
- 3 weekly intradermal MVA-EBNA1/LMP2 up to 6 cycles.
CONCLUSIONS

Nasopharyngeal carcinoma, a rare entity in Europe and U.S.

Multimodality treatment

Early stages radiotherapy

Intermediate: concurrent chemo-RT
Locally advanced: concurrent chemo-RT (induction/adjuvant)
• THANK YOU!