DEINTENSIFIED TREATMENT POSSIBILITIES IN BUCCOPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Abstract: *Besides tobacco use and heavy alcohol consumption, Human Papilloma Virus is recognised as risk factor for bucco/oropharyngeal carcinomas. In 1980s, the virus was estimated to account for 16% of OPSCCs in USA, nowadays its prevalence exceeds 60%. The HPV associated OPSCC is a different clinicopathological entity with better survival results on multimodal therapy. Preliminary results suggest that reduced intensity treatment is non inferior in survival, but better tolerated with less adverse events. We identified different strategies of reducing adverse effects of intensive treatment, as follows.1. Using different fractionation doses in radiotherapy 2. Changing cisplatin to cetuximab in concurrent chemo-radiotherapy 3. Using induction chemotherapy, followed by reduced dose chemoradiation 4. Surgery followed by deintensified chemoradiotherapy. Many radiation, chemotherapy de-escalation trials and minimally invasive surgical techniques are being evaluated. It is important to identify the ideal patient group for treatment deintensification and to define prognostic risk groups to avoid undertreating.*

INTRODUCTION

Buccopharyngeal (named also oropharyngeal) squamous cell carcinomas (OPSCCs) arise from the mucosa of the oral cavity and oropharynx.(1) Tobacco use and alcohol consumption are known risk factors for BPSCCs, in the past 20 years human papillomavirus (HPV) infection has been identified as etiologic agent for a subset of BPSCCs, specifically those that arise from the oropharynx, including base of tongue and tonsil.

In the USA, Human Papilloma Virus (HPV) was estimated to account for 16% of oral squamous cell carcinomas (OSCC) in the early 1980s, (2) now prevalence in the most recent studies exceeds 60%.(3,4,5) HPV-positive tumour status significantly improves survival, is associated with smaller primary tumours (T stage) but more advanced nodal stage, and more frequent distant metastases in multiple organs.(6,7) Furthermore, HPV-positive OPSCCs respond much better to therapy than HPV-negative OPSCCs and other head and neck cancers (5-year disease specific survival: 80% vs. 40%).(5,8) The younger patient population can live with important side effects for decades following therapy.

MATERIALS AND METHODS

We followed the international literature of the past years regarding to deintensification therapy in HPV positive head and neck squamous cell carcinomas. We were looking for randomised controlled trials investigating locally advanced (stage III/IV) HPV positive OPSCC. HPV status evaluation was made by either detecting p16 protein by immunohistochemistry (IHC), or DNA is situ hybridisation (ISH)/ polymerase chain reaction (PCR). We identified different strategies to reduce adverse effects of intensive treatment, as follows.

RESULTS

1. Using different fractionation doses in radiotherapy.
2. Changing cisplatin to cetuximab in concurrent chemo-radiotherapy.
3. Using induction chemotherapy, followed by reduced dose chemoradiation.
4. Surgery followed by deintensified chemoradiotherapy.

A retrospective analysis was made by Ang et al. in head and neck squamous cell carcinoma (HNSCC) patients in whom they compared accelerated-fractionation radiotherapy with standard-fractionation radiotherapy, each combined with cisplatin therapy. They followed the association between tumour HPV status and survival. A total of 63.8% of patients with oropharyngeal cancer (206 of 323) had HPV-positive tumours; these patients had better 3-year rates of overall survival (82.4%, vs. 57.1% among patients with HPV-negative tumours; $P<0.001$ and, after adjustment for age, race, tumour and nodal stage, tobacco exposure, and treatment assignment, they had a 58% reduction in the risk of death. The patients were classified as having a low, intermediate, or high risk of death on the basis of four factors: HPV status, pack-years of tobacco smoking, tumour stage and nodal stage.(9)

EXTREME phase III trial showed that adding cetuximab to standard chemotherapy doublet with platinum derivate and 5 FU will improve significantly the overall survival and progression-free survival in recurrent or metastatic HNSCC.(10) A post-hoc analysis made on p16 or HPV status positive cases demonstrated that the combination of cetuximab to first line agents improved survival independently of status. In recurrent and metastatic setting of oropharyngeal carcinoma (OPC) p16 or HPV status is prognostically.(11)

RTOG 1016 is a phase III trial with primary objective to determine whether substitution of cisplatin with cetuximab will result in comparable 5-year overall survival of cetuximab plus radiotherapy versus concomitant chemoradiotherapy in HPV-associated oropharynx cancer. The two drugs work differently and have different toxicity profile. It is not yet known whether radiation therapy is more effective with cisplatin or cetuximab in treating oropharyngeal cancer.(12)

Rosenthal's study results presented in 2014 at ASCO

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showed that the patients benefit more from radiotherapy + cetuximab compared with radiotherapy alone regardless of p16 status. 312 from 424 (74%) patients were evaluable for p16 protein by immunohistochemistry. In both, p16+ and p16- patients, the addition of cetuximab to radiotherapy arm (RT) improved locoregional control (LRC), overall survival (OS), and progression-free survival (PFS).(13)

The phase III international De-ESCALaTE study was designed to evaluate early and late toxicity events caused by cisplatin 100mg/m2 on days 1, 22 and 43 of radiotherapy and cetuximab initial dose of 400mg/m2 and 1 week before start of radiotherapy followed by 7 weekly doses of 250mg/m2 in HPV positive OPSCC patients, both added to radiotherapy. They will be followed up for two years, his status is open.(14)

TROG 12.01 is an Australian study that will compare the acute and chronic side effects related to treatment between the cisplatin and cetuximab regimens in HPV-associated OPSCC. Weekly Cetuximab/RT Vs Weekly Cisplatin/RT would be given with the same dose of radiation therapy over 7 weeks. Cetuximab has very different side effects to cisplatin and has been reported to result in less exacerbation of radiation related side effects. Both cetuximab and cisplatin can reduce the growth of a cancer and increase the effectiveness of radiation.(15)

The third method to deescalate treatment intensity is to give induction chemotherapy (ICT) followed by reduced doses of chemoradiation. ECOG 1308 study's primary objective is the estimation of the 2-year PFS in the reduced dose RT arm. Secondary objectives include toxicity, OS, objective response, quality of life (QOL) and correlative studies of biomarkers. Patients received neoadjuvant chemotherapy with a combination of cisplatin 75mg/m^2 on day 1 and paclitaxel 90 mg/m^2 on days 1,8, and 15 and cetuximab 400 mg/m^2 (loading dose) on day 1 of the first cycle, then maintenance dose of weekly cetuximab 250 mg/m^2. After ending 3 cycles every 3 weeks, patients underwent to a complete clinical examination of the primary site and were assessed by imaging studies. In case of clinical complete remission, they received concomitant radiotherapy with 54 Gy + cetuximab. Those with clinical partial remission or stable disease received radiotherapy in standard dose with cetuximab. Preliminary results show one-year PFS rates of 91% in the reduced RT arm and 87% in standard-dose RT arm.(16)

Researchers from University of Chicago Medicine Comprehensive Cancer Center (UCCCC) have classified head and neck cancers into five subgroups, each with unique characteristics that may help personalize treatment decisions for patients. Three types - hypoxic, basal, and classical - were not associated with HPV, had a poor prognosis, and showed unique features that may be useful to guide therapy in the future. The HPV-positive tumours, which were previously believed to be one entity, were actually two different subtypes, Dr. Seiwert said: "Our study brings us one step closer to predicting which patients will need more intensive treatment, and which patients may safely undergo a better tolerated treatment with fewer side effects".(17)

The Quarterback phase III trial was designed for HPV associated locally advanced OPSCC, in which investigators have planned to compare radiation therapy in reduced and standard radiation doses, both started after 3 cycles of neoadjuvant chmeotherapy with Docetaxel Cisplatin and 5-FU. The objective is to demonstrate that 3 year - progression free survival and locoregional control are not inferior in reduced dose chemoradiotherapy compared to standard treatment. After the induction chemotherapy, patients were evaluated for clinical, pathological and imagistic response. Patients with no response to treatment will receive standard chemoradiotherapy. Those who achieved clinical/ imagistic complete or partial remission will be randomized 2:1 to weekly carboplatin and reduced dose RT 56 Gy or standard dose RT 70 Gy. Patients with severe side effects or progression of disease, thereby not completing 3 cycles of neoadjuvant chemotherapy will be treated with surgery or standard regimen and followed for overall survival. The primary end point of local regional control and 3 year – progression free survival is equivalent, but the investigators will follow them for 5 years.(18)

Results of postoperative treatment strategies are also analysed. Post Operative Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related, p16+ Oropharynx Cancer (ADEPT) evaluates the intensity of adjuvant therapy. Patients have had all known disease removed surgically by a minimally invasive approach and have had extracapsular spread in their lymph nodes. They can consent to participate in either the randomized (physician chooses radiotherapy arm or radiotherapy & cisplatin arm) or non-randomized (patient chooses radiotherapy arm or radiotherapy & cisplatin arm) pathways. After the surgery, they receive either radiation alone, or radiation and weekly cisplatin during therapy. Patients are then followed for cancer, functional and quality of life outcomes.(19)

PATHOS is another ongoing phase II/III trial which evaluates adjuvant treatment strategies after surgery in HPV associated head and neck squamous cancers. All patients underwent transoral surgery and neck lymphadenectomy and were distributed in groups based on the histopathologic risk factors of recurrence. The high risk group patients will be randomised to receive radiotherapy alone or post-operative chemoradiotherapy. The intermediate risk group patients will be randomised to receive radiotherapy in reduced doses or standard dose radiotherapy. The low risk group patients will not receive any treatment.

There is a possibility for this phase II PATHOS trial to proceed to a non-inferiority phase III trial, having a strong primary endpoint of overall survival.(20)

ECOG 3311 randomised trial will follow HPV positive OPSCC patients in 4 groups. A will undergo surgery, B surgery + low dose IMRT for 5 weeks, C surgery + standard dose IMRT for 6 weeks and D surgery +standard-dose IMRT daily, days 1-5 for 6 or 7 weeks. As chemosensitiser for radiotherapy, patients receive intravenously 7 cycles of weekly platinum, either cisplatin over 60 minutes or carboplatin over 30 minutes. The ongoing study primary aim is PFS rate.(21)

DISCUSSIONS

At the 57th Annual American Society for Radiation Oncology (ASTRO) meeting in San Antonio in October 2015, there were presented the results of a phase II prospective study designed at University of North Carolina School of Medicine. Dr Chera et al. evaluated reduced intensity chemoradiotherapy among 43 patients with favourable risk HPV associated OPSCC. After treatment completion, patients underwent biopsies at tumour site or lymph nodes in order to determine treatment efficiency; they were evaluated for quality of life by standardised questionnaires, made functional testing of esophagus motility and swallowing. Of the 43 patients studied, 37 of them (86%) had pathological CR. The six cases that did not show pCR were limited to microscopic areas of residual cancer. Results of QoL were far superior to standard treatment and returned to baseline levels 1 year later. The deintensified regimen consisted of 10 Gy reduction in the total dose of radiation and the dose of cisplatin was reduced approximately 40% to 30 mg/mp administered in 6 weekly doses.(22)

Standard chemotherapy protocols result in excellent cancer control and survival among patients, but they produce

substantial adverse events, such as dry mouth, painful inflammation, tooth decay, difficulties in talking and swallowing, permanent feeding tubes. Many radiation and chemotherapy de-escalation trials are underway. Minimally invasive surgical techniques are also being evaluated. It is important to identify the ideal patient group for treatment deintensification and to define prognostic risk groups to avoid undertreating the poorer-risk subset in HPV positive OPSCC, and validated biomarkers are needed to identify patients with the best prognosis.

CONCLUSION

Currently, less intense treatment is an option only in the setting of clinical trials.

REFERENCES

1. Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck. 2007;29:779-792.
2. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. J Natl Cancer Inst. 2005;97:1407-1427.
3. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer-systematic review and meta-analysis of trends by time and region. Head Neck. 2012; (Epub 2012/01/24). doi: http://dx.doi.org/ 10.1002/hed.22015.
4. Rysera M, McGoff K, Herzog D, Sivakoff D, Myers E. Impact of coverage-dependent marginal costs on optimal HPV vaccination strategies. EPIDEMics. 2015;173:1-16. http://dx.doi.org/10.1016/j.epidem.2015.01.003.
5. Dalianis T. Human papillomavirus (HPV) and oropharyngeal squamous cell carcinoma. Presse Med. 2014;43:429-434.
6. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral Oncology. 2014;50:565-574.
7. Sood A, McIlwain W, O'Connell B, Nguyen S, Houlton J, Day T. The association between T-stage and clinical nodal metastasis in HPV-positive oropharyngeal cancer. Head and Neck Medicine. 2014;35:463-468.
8. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. Preventive Medicine. 2011;53:S5-S11.
9. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;1:363(1):24-35. doi: 10.1056/NEJMoa0912217.
10. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116-1127. doi: 10.1056/NEJMoa0802656.
11. Vermorken JB, Psyrri A, Mesia R, Peyrade F, Beier F, de Blas B, et al. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: Retrospective analysis of the phase III EXTREME trial. Ann Oncol. 2014;25:801-807. doi: 10.1093/annonc/mdt574.
12. Phase III trial of radiotherapy plus cetuximab versus chemoradiotherapy in HPV-associated oropharynx http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/deescalate/trialsummary/.
13. Rosenthal DI, Harari PM, Giralt J, Bell D, Raben D, Liu J et al. Impact of p16 status on the results of the phase III cetuximab (cet)/radiotherapy (RT) J Clin Oncol. 2014;32:5s (suppl; abstr 6001).
14. De-ESCALaTE Determination of epidermal growth factor receptor – inhibitor (cetuximab) versus standard chemotherapy (cisplatin) early and late toxicity events in human papillomavirus-positive oropharyngeal squamous cell carcinoma http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/deescalate/trialsummary/.
15. A randomised trial of weekly cetuximab and radiation versus weekly cisplatin and radiation in good prognosis locoregionally advanced HPV-associated oropharyngeal squamous cell carcinoma. https://clinicaltrials.gov/ct2/show/NCT01855451?term=TROG+12.01&rank=1.
16. Marur S, Lee J, Cmelak A, Zhao W, Westra WH, Chung CH et al. ECOG 1308: A phase II trial of induction chemotherapy followed by cetuximab with low dose versus standard dose IMRT in patients with human papilloma virus (HPV)-associated resectable squamous cell carcinoma of the oropharynx (OPSCC) J Clin Oncol. 2013;31:6005.
17. Keck MK, Zuo Z, Khattri A, Stricker TP, Brown CD, Imanguli M et al.Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes. Clin Cancer Res. 2015;21(4):870-81. doi: 10.1158/1078-0432.CCR-14-2481. Epub 2014 Dec 9.
18. The Quarterback Trial. https://clinicaltrials.gov/ct2/show/NCT01706939?term=quarterback+trial&rank=1.
19. Adjuvant Therapy De-Intensification Trial for Human Papillomavirus-Related, p16+ Oropharynx Cancer (ADEPT) (accessed on13 October 2014)); https://clinicaltrials.gov/ct2/show/NCT01687413.
20. PATHOS trial: Post-Operative Adjuvant Treatment for HPV-Positive Tumours. https://clinicaltrials.gov/ct2/show/NCT02215265.
21. Transoral surgery followed by low-dose or standard-dose radiation therapy with or without chemotherapy in treating patients with HPV positive stage III–IVA oropharyngeal cancer (ECOG 3311) https://clinicaltrials.gov/ct2/show/NCT01898494.
22. Chera BS, Amdur RJ, Tepper J, Qaqish B, Green R, Hayes N, et al. A Prospective Phase II Trial of De-intensified Chemoradiotherapy for Favourable-Risk HPV-associated Oropharyngeal Squamous Cell Carcinoma, Radiation Oncology 2015, http://dx.doi.org/10.1016/j.ijrobp.2015.08.033.