DAHANCA 28a

Phase I/II study of acc. hyperfractionated RT, cisplatin and nimorazole in P16-LAHNSCC

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Published in:
Radiotherapy and Oncology

DOI (link to publication from Publisher):
10.1016/S0167-8140(19)30207-5

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Proffered papers: Proffered papers 3

OC-040 Nomogram for cumulative cisplatin dose for LAHNC receiving tri-weekly high-dose cisplatin CCRT

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Purpose or Objective
Tri-weekly high-dose cisplatin concurrent chemo-radiotherapy (CCRT) is a standard regimen for locally advanced head and neck cancer (LAHNC) in both definitive and postoperative settings. However, this treatment causes severe acute toxicity in over three-quarters of patients. Consequently, many patients cannot tolerate high-dose cisplatin and receive lower cisplatin dose than expected, and thus have compromised outcome. Alternative treatment (weekly cisplatin or cetuximab) may be beneficial to these high-dose cisplatin-intolerant patients. Limited data identify the risk factors of high-dose cisplatin intolerance. The goals of this study are to assess cisplatin tolerance, to identify the related risk factors, and to develop a nomogram for patient selection.
Material and Methods
Between 2010 and 2017, we retrospectively assessed consecutive patients who had received curative definitive CCRT with tri-weekly high dose cisplatin in a single tertiary institution. Patient characteristics (age, gender, performance score, Charlson Comorbidity Index (CCI), tumor site, stage, BMI, Hgb, albumin, eGFR, uric acid, neutrophil count, diabetes mellitus, hypertension, cirrhosis, smoking, alcohol consumption) were collected. Logistic regressions were performed for each factor to predict the cumulative cisplatin dose more than 200 mg/m^2 or not. A step-wise multivariate model was constructed to generate a nomogram. Model discrimination is evaluated using area under ROC curve (AUC) and Akaike Information Criterion (AIC). Overall survival was plotted with Kaplan-Meier method, stratified by cumulative cisplatin dose of 200 mg/m^2. The survival results were compared by adjusted Cox regression.
Results
A total of 508 patients were assessed; 316, 69, 71, and 52 patients had NPC, oropharyngeal cancer, hypopharyngeal cancer, and oral cavity cancer, respectively. The median follow-up time was 38.7 months. Three hundred and forty-two (67.3%) patients had received cumulative cisplatin dose more than 200 mg/m^2. Age, alcohol consumption, CCI, Hgb, and neutrophil count were significantly associated with cisplatin cumulative dose (Table 1). Incorporating these five factors, the nomogram (Fig. 1) achieved good concordance (AUC and AIC was 0.74, and 756). A statistically significant association between cumulative cisplatin dose and survival was observed.

Figure 1

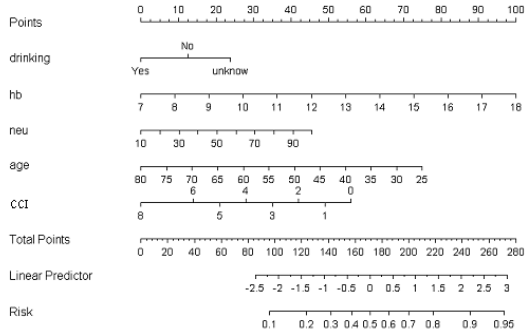

Table 1:Multi-variate logistic regression for cumulative cisplatin dose >= or < 200 mg/m2

	OR	95% CI	p value
Alcohol (Yes vs No)	0.692	0.508-0.943	0.0198
Hgb	1.306	1.208-1.414	<0.0001
Neutrophil count	1.015	1.003-1.027	0.0152
Age	0.961	0.946-0.976	<0.0001
CCI	0.814	0.698-0.942	0.0069

Conclusion
The nomogram achieved an optimal prediction of cumulative cisplatin dose during CCRT in LAHNC. By applying this model, the risk of treatment intolerance can be determined, which can lead to better patient selection for tri-weekly high-dose cisplatin CCRT.

OC-041 DAHANCA 28a: Phase I/II study of acc. hyperfractionated RT, cisplatin and nimorazole in P16-LAHNSCC

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Purpose or Objective
Despite encouraging results using primary radiotherapy (RT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC), patients with p16-negative LAHNSCC continues to have a poor prognosis. This group has mostly tobacco- and alcohol-related cancer and consequently comorbidities which make treatment intensification challenging. The aim of this study was to assess the feasibility and efficacy of dose escalation using accelerated, hyperfractionated RT with nimorazole and weekly cisplatin in patients with p16-negative LAHNSCC and varying degrees of risk factors.
Material and Methods
Patients with increasing number of co-morbidities (as defined by the Charlson co-morbidity score) were allocated to primary accelerated hyperfractionated RT, 76Gy/56fx, 10fx/week, concomitant weekly cisplatin (40mg/m^2) and nimorazole according to the DAHANCA guidelines. The data analysis was performed as intention-to-treat. Primary endpoint was loco-regional control. Secondary endpoints were overall survival and toxicity. No

elective neck dissections were allowed. With respect to dose coverage, spatial analyses of failure sites were made for patients with residual or recurrent disease.

Results

From February 2013 to November 2015, 31 patients were accrued. The median age was 61 years and 77% were males. All had WHO performance 0 (65%) or 1 (35%), most were current smokers (81%, median 41 pack years) and had increasing co-morbidity scores from 0 to 2. All had p16-negative, LAHNSCC; mostly stage IV (90%) pharynx carcinomas (74%). The proportion of patients receiving RT as planned was 94%, whereas compliance to full treatment with cisplatin and nimorazole was lower, 58% and 74%, respectively. Nine loco-regional recurrences were detected with a median follow-up time of 27 months (range 0-61), and two of these were in patients, who terminated treatment prematurely. A pattern-of-failure analysis by co-registering planning and recurrence CT showed that all loco-regional recurrences were in the high dose CTV. One patient presented with distant metastases only. The three-year actuarial loco-regional tumor control was 70%, whereas overall survival was 58%. Almost 80% needed tube-feeding during treatment, but at two months after end of therapy, this was reduced to 50% and at 6 months to 17%. At end of therapy, 20% experienced grade≥3 dysphagia and 15% grade≥3 mucositis. The proportion of patients reporting severe late dysphagia was 16% and 42% reported late, moderate to severe dryness of the mouth.

Conclusion

Accelerated hyperfractionated RT with concomitant low-dose cisplatin and nimorazole is feasible in patients with locally advanced p16-negative head and neck squamous cell carcinoma presenting in good general health. Outcome in terms of loco-regional tumor control at 3 years is encouraging with an anticipated and acceptable level of acute and late toxicity.

OC-042 Genomic characterization of oral premalignant lesions to identify high-risk molecular clusters

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Purpose or Objective

Oral premalignant lesions (OPLs) represent the most common oral precancerous conditions. One of the major challenges in this field is the identification of OPLs at higher risk for oral squamous cell cancer (OSCC) development, possibly revealing molecular pathways to be regulated before their malignant transformation. Gene expression analysis represents a useful tool to evaluate genomic pathways of OPLs with such a clinical implication.

We aimed at dissecting genomic characteristics of OPLs to identify high-risk molecular clusters.

Material and Methods

By an unsupervised clustering analysis, we previously disclosed 6 molecular subtypes in a large meta-analysis comprising 1386 head and neck SCC cases (De Cecco et al, 2015).

We investigated whether these molecular patterns were already present in OPLs, by applying this model to a gene-expression data set of patients enrolled in a clinical chemoprevention trial, which employed malignant transformation as the primary endpoint (Saintigny et al, 2011).

Gene expression profile was measured in 86 of 162 OPL patients. These cases were then stratified accordingly to our subtype classification applying the PAM signature including 2843 genes.

Results

Overall, 2 cases (2.3%) were classified as Cluster (Cl) 1-HPV, 10 (11.6%) as Cl2-Mesenchymal, 11 (12.8%) as Cl3-Hypoxia, 21 (24.4%) as Cl4-Defense Response, 11 (12.8%) as Cl5-Classical, and 31 (36%) as Cl6-Immunoreactive. This molecular stratification was then correlated with oral cancer-free survival as calculated by Kaplan-Meyer analysis.

Patients stratified as Cl3-Hypoxia and Cl5-Classical showed the worst clinical behaviors, with a higher risk of malignant transformation (log rank, p=0.0052).

Conclusion

Dissecting the pathways of OPLs by evaluation of the different clusters obtained with gene expression profiling, we identified 2 clusters at higher risk of oral cancer development, namely Hypoxia and Classical clusters. Further researches are needed to improve the identification of adequate prognosticators in OPLs and to find molecular pathways to be addressed for reduction of the risk of cancerization.

OC-043 HNSCC in elderly frail patients treated by hafnium oxide nanoparticles activated by IMRT

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Purpose or Objective

Hafnium oxide nanoparticles, NBTXR3, were developed to augment tumor-localized high energy deposit once activated by ionizing radiation such as Intensity Modulated Radiation Therapy (IMRT) and thus to increase tumor cell death compared to the same dose of radiation. NBTXR3 is characterized by a single intratumoral (IT) administration and fits into standard radiotherapy schedule with no change in patient's care pathway, treatment protocol or equipment. A phase I trial is currently evaluating NBTXR3 in elderly patients (pts) with locally advanced head and neck squamous cell carcinoma (HNSCC) of the oral cavity and oropharynx not eligible for cisplatin or intolerant to cetuximab [NCT01946867].

Material and Methods

In this phase I open-label, non-randomized trial, elderly frail pts (65 years and older) were treated with an IT injection of NBTXR3 followed by IMRT (70 Gy in 35 fractions over 7 weeks) with a follow-up period until disease progression or study cut-off date. The study was designed as a 3 + 3 escalation dose with tested NBTXR3