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OROPHARYNGEAL SQUAMOUS CELL CARCINOMA TREATED CONCURRENTLY WITH CETUXIMAB: A CASE REPORT OF INTOLERANCE TO CISPLATIN IN YOUNG AGE

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Keywords: concurrent chemoradiotherapy, cisplatin, cetuximab; human papilloma virus; base of tongue; oropharyngeal carcinoma.

Summary

Squamous cell carcinoma of the oropharynx is a common case of head and neck cancer related to human papillomavirus. We present a case of moderately (G2) differentiated squamous cell carcinoma, which responded well to concurrent radiotherapy with cetuximab after intolerance of cisplatin. A 37-year-old woman referred to our hospital for a locally advanced cancer of the base of tongue. Physical examination revealed an ulcerative tumor with spread to the supraglottic structures, and swelling of the right side cervical lymph node at group IIA. The histological diagnosis from a biopsy specimen was moderately differentiated p16 positive squamous cell carcinoma. The patient underwent cisplatin-based concurrent chemoradiotherapy. Two - three weeks after receiving an intravenous cisplatin dose 100 mg/m^2 for the first day of chemorradiation, the patient presented with profound bilateral sensorineural hearing loss. The cisplatin-based chemotherapy had changed to alternative agent. The patient continuously underwent concurrently radiation with cetuximab without the break of radical radiotherapy course. The patient experienced partial recovery of hearing after radical treatment of cancer. Complete clinical and radiological response of oropharyngeal squamous carcinoma was achieved.

Conclusions. Toxicity with only one standard dose of cisplatin can be profound also in young age. This risk should be addressed when counseling patient prior to initiation of treatment. In case of platinum ineligibility, replacing cisplatin with less toxic agent cetuximab may be taken into consideration for p16 positive carcinoma of the oropharynx.

Introduction

The epidemiology of head and neck squamous cell carcinoma (HNSCC) has shifted dramatically over the last 50 years, as smoking-related HNSCCs decrease in incidence while human papillomavirus (HPV)-related cancers rise. Head and neck squamous cell carcinomas related to HPV are generally more sensitive to chemotherapy and have better prognoses [1,2,3]. The meta - analysis of chemotherapy in head and neck cancer demonstrated a 6.5% absolute improvement in 5-year overall survival with concurrent chemo-radiotherapy (CCRT) over radiotherapy (RT) alone. Concurrent high-dose cisplatin (100 mg/m2 on days 1, 22 and 43 during RT) was identified as the most effective regimen [4]. Definitive concurrent chemoradiation with high-dose cisplatin is therefore regarded as the preferred choice in the European and NCCN clinical practice guidelines for the treatment of fit patients with loco-regionally advanced squamous cell head and neck cancer [5].

Cetuximab, a molecular agent targeted against epidermal growth factor receptor, is reported to have significant efficiency in treatment of head and neck squamous cell carcinoma [6]. The use of cetuximab as an alternative to high-dose cisplatin, the recommendations in Europe differ from those formulated in the NCCN guidelines [5,7]. There has been no randomized phase III trial reported that compares cetuximab/RT with cisplatin-based concurrent chemorradiation (CCRT) [7].

We present here a case of locally advanced p16 positive carcinoma of the base of tongue r/cT3N1M0 that completely responded after concurrent chemorradiation after first cycle of cisplatin has changed effectively due to sensorineural hearing loss to concurrent radiation with cetuximab.

Case report

A 37-year-old woman was referred to our hospital in April 2019, because of a tumor on the right-side of her base

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of tongue. She had no history of smoking or alcohol-related problems. Her nutrition was normal. Physical examination showed an ulceration of overlying mucosa and hard tumorous lesion on the right side of the base of the tongue, with a size of approximately 25×20 mm. There were also an enlarged cervical lymph node in the upper jugular region (IIA group). Computed tomography and magnetic resonance imaging (MRI) revealed a tumour diffusely invading into in to the right side base of tongue. The cervical lymph node (II A) was uniformly enlarged and were impinging on the internal jugular vein and common carotid artery (Fig. 1A). By positron emission tomography, we revealed additional information of primary tumour extension to the supralaryngeal structure – aryepiglottic space and lingual surface of epiglottis (cT3). No more distant metastasis or any other primary tumor was observed on PET-CT. (Fig. 1B).

Under a clinical diagnosis of tongue cancer cT3N1M0, incisional biopsy was performed. The specimen was a tumor sample consisting of moderately differentiated p16 positive squamous cell cancer cells.

We initially discussed with surgeons about possibility to perform surgery to the patient but did not obtain consent, because of the possibility of functional issues. Therefore, standard radical concurrent chemoradiotherapy with cisplatin had planned.

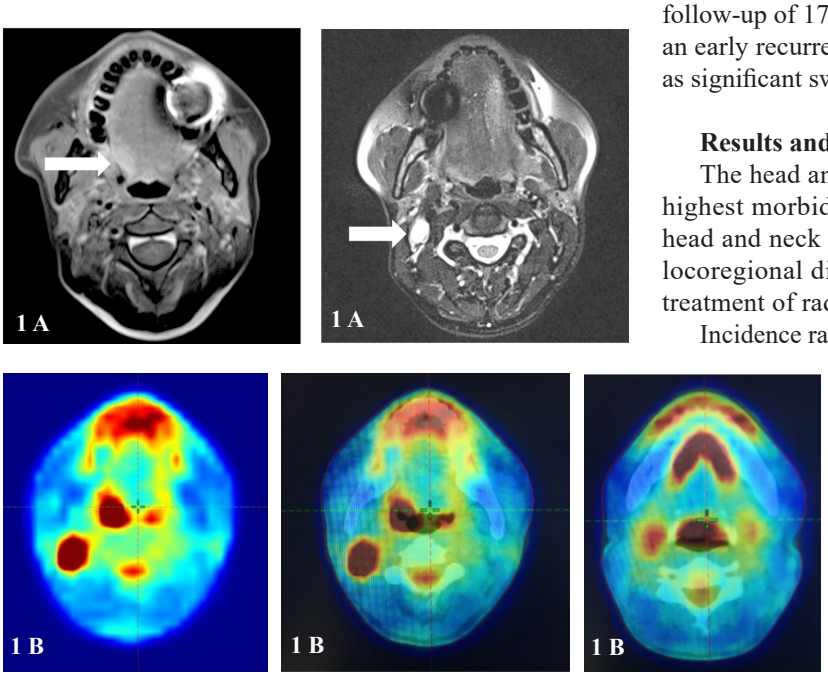

Fig. 1. Magnetic resonance imaging (A) and PET-CT (B). A primary tumour diffusely invading into the right side of base of tongue with extension to lingual surface of epiglottis on the PET CT. The cervical lymph node near the internal jugular vein and common carotid artery was uniformly enlarged.

The total dose of 70 Gy in 35 fractions over 7 weeks with IMRT/VMAT prescribed. The patient received 54 Gy /27 fractions to the lymhnodes followed by a sequential boost of 16 Gy /8 fractions to gross tumor volume as well as 3 cycles of cisplatin at 100 mg/m2 during RT.

After two and a halve week after first treatment cycle with cisplatin, the patient developed profound bilateral sensorineural hearing loss (SNHL) (Fig. 2) and chemotherapy was stopped.

The cisplatin-based chemotherapy had changed to alternative agent. The patient continuously underwent concurrently radiation with weekly cetuximab at an initial dose of 400 mg per square meter of body-surface area, followed by 250 mg per square meter weekly without the break of radical radiotherapy course. Despite medical treatment, the patient experienced partial recovery of hearing after treatment of cancer. Moreover, it could be related to the radiotherapy dose to the cochlea, but the mean planned dose (Gy) to these organs at risk was low: to the right cochlea – 21,58 Gy and 16,98 Gy to the left side. No severe other adverse events occurred. Only significant leukopenia was observed. Patient had grade 2 acute radiation mucositis and dermatitis after treatment.

The tumor and the metastatic lymph node showed complete response after completing of treatment (Fig.3). During follow-up of 17 months after treatment was no evidence of an early recurrence or any other functional disorders such as significant swallowing problems.

Results and discussion

The head and neck squamous cell carcinoma have the highest morbidity, accounting for 85% death among all head and neck cancers [8]. Most patients have advanced locoregional disease at diagnosis and require combined treatment of radiotherapy and systemic therapy [9].

Incidence rates of treatment toxicity such as SNHL after RT and CRT varied considerably, with percentages ranging from 0% to 43% and 17% to 88%, respectively. Factors that influenced the risk of SNHL were radiation dose to the cochlea, follow-up time, age, baseline hearing level, and cisplatin dose. The wide range of SNHL incidence rates makes it impossible to draw any conclusions on the severity of RT and CRT induced ototoxicity [10]**.** Studies on the incidence and severity of hearing loss in head and neck cancer patients are limited, but those studies suggest that the risk of hearing loss is greater with higher-

dose regimens of cisplatin [11].

The use of cetuximab as an alternative to high-dose cisplatin and has been increasingly used to treat patients who concern about the toxicity of platinum chemotherapy. The recommendations in Europe differ from those formulated in the NCCN guidelines [5]. There has been no randomized phase III trial reported that compares cetuximab/RT with cisplatin-based CCRT and the only data available are those reported from a phase III trial, comparing cetuximab/RT with RT alone [12], and from a randomized phase II study, comparing cetuximab/RT with cisplatin-based CCRT after cisplatin-based induction chemotherapy [12,13,14].

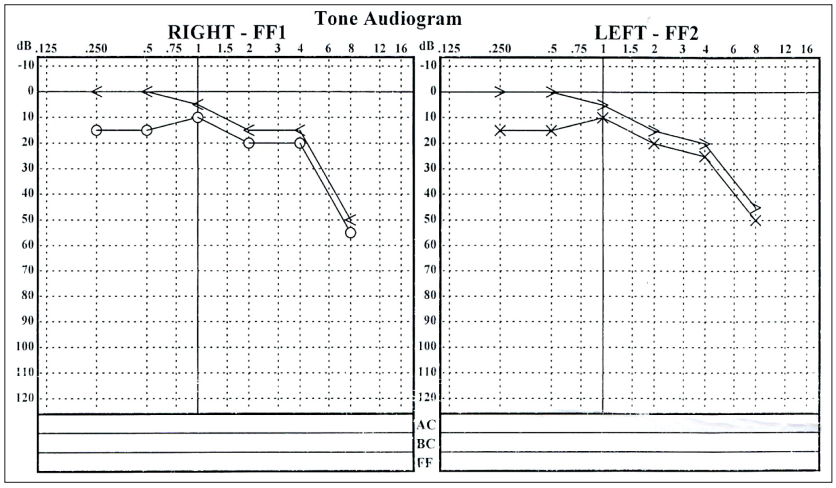

Fig. 2. Tone audiogram of the patient shows profound bilateral sensorineural hearing loss after I cycle of Cisplatin.

In addition, a recently published literature-based meta-analysis on platinum-based CCRT versus cetuximab/RT showed significantly better 2-year results with respect to overall survival, progression-free survival and loco-regional control [14]. The lack of sufficient data addressing these issues confounds decision making. Yet, the choice for the most optimal treatment for an individual patient is a critical issue and therefore a better selection of patients who might need less aggressive therapy versus those who might need more is another important area of research. A comprehensive literature and a meta-analysis of data shows us that the concurrent cetuximab may still be administered to patients who cannot tolerate cisplatin [14,15].

The treatment plan for the patient described in this report was restricted by the toxicity of the CCRT with cisplatin after the first cycle despite young age of patient. The patient tolerance to the bioradiotherapy we decided to follow was acceptable. The tumor and metastatic lymph node showed complete response after completing of radical treatment (Fig.3). During follow-up of 17 months after treatment clinically and radiologically was no evidence of an early recurrence or any other functional disorders such as significant swallowing problems. Therefore, we suggest that concurrent bioradiotherapy with cetuximab is one of the option for p 16 positive carcinoma of the head and neck cancer replacing cisplatin in case of intolerance.

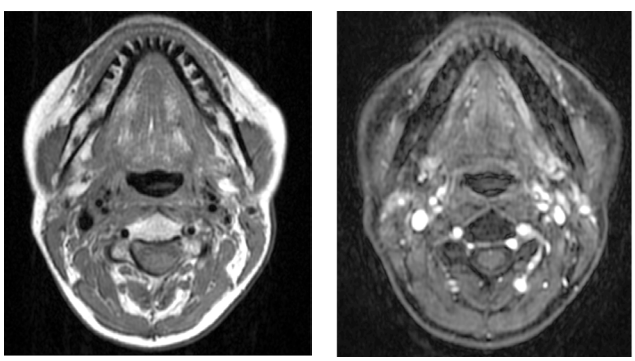

Fig. 3. Magnetic resonance imaging after CCRT shows complete response of primary tumour and metastatic lymphnode

Conclusions

Toxicity with only one standard dose of cisplatin can be profound also in young age. This risk should be addressed when counseling patient prior to initiation of treatment. In case of platinum ineligibility, replacing cisplatin with less toxic agent cetuximab may be taken into consideration for p 16 positive squamous cell carcinoma of the oropharynx.

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SUTAPTINIS BURNARYKLĖS VĖŽIO BIOSPINDULINIS GYDYMAS, JAUNAI PACIENTEI PO PIRMO CISPLATINOS CIKLO NUSTAČIUS ABIPUSĮ NEUROSENSORINĮ KLAUSOS NERVO PAŽEIDIMĄ

A. Plieskienė, A. Česas

Raktažodžiai: sutaptinis chemospindulinis gydymas, cisplatina, cetuksimabas, žmogaus papilomos virusas, burnaryklės vėžys.

Santrauka

Radikalus sutaptinis chemospindulinis gydymas dažnai skiriamas vietiškai išplitusio galvos-kaklo vėžio gydymui, kai radikali operacija neįmanoma arba siekiama geresnės funkcijos po gydymo. Plokščialąstelinės p16 teigiamos karcinomos radikalaus chemospindulinio gydymo rezultatai yra patys geriausi, tačiau klinikinėje praktikoje susiduriame su cisplatinos toksiškumu, kuris pasireiškia net ir jauname amžiuje.

Straipsnyje pristatomas klinikinis atvejis, kai po pirmojo chemoterapijos ciklo, skiriant sutaptinį vietiškai išplitusio burnaryklės vėžio chemospindulinį gydymą, pasireiškė abipusis neurosensorinis klausos nervų pažeidimas, lėmęs pacientės apkurtimą. Nutraukus cisplatinos skyrimą, radikali radioterapija toliau buvo skiriama kartu su cetuksimabu. Aktyviai stebint pacientę po biospindulinio gydymo, per 17 mėn. nebuvo nustatyta vietinio burnaryklės vėžio atkryčio ir metastazių. Manome, kad gydant vietiškai išplitusius galvos kaklo piktybinius navikus radikalia radioterapija su cisplatina, nustačius sunkų šalutinį poveikį ir netoleruojant chemoterapijos, cisplatiną galima pakeisti bioradioterapija su cetuksimabu.

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