Chapter 8
Head and Neck

Adorján F. Kovács

The overwhelming majority of head and neck malignancies are squamous cell carcinomas of the oral cavity, pharynx, and larynx. Three modalities of therapy have established roles in the treatment of carcinoma of the head and neck: chemotherapy, radiation therapy, and surgery. The choice of modality depends upon factors such as the site and extent of the primary lesion, the likelihood of complete surgical resection, the presence of lymph node metastases, and others. Traditionally, smaller lesions (T1–T2) are quite effectively treated by either surgical excision or irradiation, whereas more advanced cancers (stage III–IV) are treated with combined modalities. In recent years, chemoradiation has become an accepted alternative to surgery and postoperative radiation therapy.

Among the many chemotherapy agents developed, cisplatin has proven efficacy on head and neck carcinomas. However, in chemo-

A.F. Kovács
Private Practice, Goethe University Frankfurt a. M.,
64569 Nauheim, Germany
e-mail: profkovacs@googlemail.com

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therapy trials for head and neck tumors, the highest rates for locoregional control and survival have been achieved when chemotherapy has been administered concomitantly with radiation therapy. To date, single-agent intravenous (IV) cisplatin chemoradiation still was not proven inferior to IV polychemotherapy and irradiation which offers the possibility to use cisplatin more effectively.

By increasing drug dosage, drug resistance can be overcome. However, a practical limitation to this strategy is toxicity to normal cells (mainly renal and gastrointestinal). Clinically, it is possible to deliver higher concentrations of cisplatin through pharmacologic and technical manipulations. One strategy is through intra-arterial (IA) delivery. In the case of cisplatin, increase of plasma clearance can be accomplished by using the neutralizing agent thiosulfate. Thiosulfate reacts covalently with cisplatin to produce a complex that is still soluble but totally devoid of either toxicity or antitumor activity. The extent of reaction is a function of the concentration of both agents, and molar thiosulfate/cisplatin ratios in excess of ten are required. Thiosulfate is extensively concentrated in the urine leading to excellent protection against cisplatin-induced nephrotoxicity.

The head and neck region is particularly well suited for regional chemotherapy. Most patients who present with advanced carcinomas of the upper aerodigestive tract do not have demonstrable distant metastases. Furthermore, approximately one half of the patients have large, bulky lesions confined to one anatomic site, such as the tongue, pharyngeal wall, nasal cavity, and paranasal sinuses or larynx. Although many of these patients may have metastases to the regional cervical lymph nodes, it is usually uncontrolled tumor within the primary site that presents an immediate threat to life. The blood supply to these tumors is primarily derived from branches of the external carotid artery. Significant technical advances in angiography now permit repeated safe superselective micro-catheterization of the dominant nutrient artery using a coaxial approach, which serves to decrease blood flow and further increase therapeutic advantage.

The feasibility of selective IA cisplatin infusion for head and neck tumors has been established, and a number of studies have been reported. With respect to survival, randomized studies have to be considered because according to contemporary conviction only they can produce level 1 evidence. There is one such trial proving a survival benefit of *regional induction chemotherapy*. The EORTC conducted it to evaluate the role of preoperative IA chemotherapy on survival of patients with tumors of the oral cavity and oropharynx. Two hundred and twenty-two eligible subjects were randomized between surgery and preoperative IA chemotherapy. This latter group received vincristine and bleomycin from the catheter placed retrograde into the external carotid artery from the superficial temporal artery. The overall survival showed a statistically significant difference ($P = 0.048$) for floor of the mouth but not for posterior oral cavity and oropharynx groups. In the floor of the mouth group, median survival in the chemotherapy arm was estimated at 7 years compared with 3 years in the surgery arm. In the posterior oral cavity and oropharynx group, median survival was estimated at 3 years in both treatment arms [1].

The largest trial sequence using regional chemotherapy as *induction* for patients with oral and oropharyngeal cancers of all stages was conducted by Kovács and coworkers. They successfully integrated regional chemotherapy in a multimodality treatment and could demonstrate a survival benefit for patients with resectable tumors compared to a prognostic index [2]. They also proved that chemoembolization can safely be carried out in certain areas of the head and neck (floor of mouth, anterior oral tongue, mandibular alveolar ridge). A new preparation and effect format of cisplatin was introduced by using a highly concentrated aqueous crystal suspension with microembolizing properties, and this method alone is compared to a combination using degradable starch microspheres (DSM) in the treatment of oral and oropharyngeal squamous cell carcinomas. DSM were chosen because occlusion of the vessels endures only maximum

1–2 h [3]. As an alternative procedure for TACE, the authors were using the suspension of cisplatin crystals alone [4].

The most comprehensive trial sequence of *intra-arterial chemoradiation* was conducted by Robbins and coworkers. They succeeded in accruing enough patients for valid statistical evaluation and maintained a consistent reproducible method (RADPLAT = radiotherapy and concomitant intra-arterial cisplatin). Results were impressive with regard to all possible end points, even in multicenter studies [5]. Having started as treatment for unresectable patients, IA chemoradiation was developed as a regimen for organ preservation. Other study groups confirmed these favorable results. Based on these promising results, a randomized trial was conducted in the Netherlands comparing RADPLAT with IV chemoradiation therapy [6]. Two hundred and thirty-nine subjects from five hospitals, with (functional) inoperable head and neck cancer, were randomly assigned to receive radiotherapy (70 Gy/35f for 7 weeks) combined with either four courses of IA cisplatin infusion on days 2, 9, 16, and 23 or IV cisplatin on days 1, 22, and 43. This trial could not prove a significant advantage of intra-arterial chemoradiation with respect to survival. (Other studies seemed to support this result [7].) Because a high proportion of subjects in the trial received the less effective technique of bilateral infusion, many questions remain about the value of this and comparable results. Moreover, significantly fewer problems with nausea and vomiting occurred in patients treated with IA chemoradiation, which should justify the higher interventional time and effort of IA chemotherapy as compared to the simple IV procedure. It is a pity that quality-of-life issues are neglected in such cases.

Japan belongs to the countries with the highest experience with intra-arterial chemotherapy. It was Yokoyama who first reported superselective high-dose cisplatin infusion with simultaneous IV infusion of thiosulfate to neutralize cisplatin toxicity

in 1998 in Japan. He reported that large tumors were gone with this therapy and high-dose weekly cisplatin infusion did not cause serious side effects, which surprised Japanese head and neck surgeons and radiation oncologists. Since then, IA chemotherapy has gained recognition and popularity again in Japan because the long history with the therapy has made it easy to accept. There are variations of the prototypic Robbins method with higher doses of cisplatin [8] and new combinations and agents, e.g., [8, 9]. New radiation techniques are also evaluated in combination with IA chemotherapy [9].

Too often, the fundamental pharmacologic principles of IA therapy have been ignored, and response rates and survival rates have not been convincingly superior to those obtained with IV cisplatin. Enthusiasm for IA chemotherapy in head and neck cancer has also been thrown back by technical problems related to the placement of infusion catheters. Most studies involved percutaneous catheterization of the external carotid with or without implantable infusion pumps and indwelling catheters, and this was problematic because of infection and thrombosis. Significant technical advances in vascular radiology techniques now permit safe repetitive superselective catheterization of the smaller nutrient arteries of the tumor.

8.1 Study Results

Kovács and Turowski (2002) [3]

Concept	Chemoembolization of oral and oropharyngeal cancer using a high-dose cisplatin crystal suspension and degradable starch microspheres (DSM)
N	32
Inclusion criteria	Histology confirmed, previously untreated, primary squamous cell carcinomas

Therapy	IA without DSM, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s) IA with DSM, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s) at the end of the total amount of cisplatin minus 5 mL; 1 mL DSM (60 mg DSM) were mixed with 5 mL cisplatin (25 mg cisplatin)and 4 mL contrast medium and were administered until occlusion of the vessels One cycle of IA high-dose chemoembolization per patient (in case of PR max. Two cycles)				
Results	Response rate was assessed 3 weeks after treatment				
		CR	PR	SD	PD	T stage (*n*)
	With DSM (*n* = 15)	5 (33.3%)	8 (53.3%)	2 (13.4%)	0	T1 = 2; T2 = 5; T3 = 1; T4 = 7
	Without DSM (*n* = 17)	3 (17.6%)	8 (47.1%)	6 (35.3%)	0	T1 = 0; T2 = 4; T3 = 2; T4 = 11
	Overall (*n* = 32)	8 (25%)	16 (50%)	8 (25%)	0	
Toxicity	Toxicity of chemoembolization: Nausea (grade I + II), 15.65%; pain (grade I + II), 71.9%; leukocytosis (grade I), 56.25%; swelling (grade I), 25%				
Conclusions	Chemoembolization with DSM prolonged antitumor activity and increased overall response in squamous cell carcinoma patients				

Kovács (2004) [2]

Concept	Long-term survival of patients with resectable oral and oropharyngeal cancer treated with IA chemotherapy and surgery
N	52
Inclusion criteria	Histology confirmed, previously untreated, resectable, primary squamous cell carcinomas stage I–IV
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s) One to two cycles of neoadjuvant IA chemotherapy followed by radical surgery

Results	Response after first cycle: CR, 20 pts. (38%); PR, 16 pts. (31%); SD, 16 pts. (31%) Mean follow-up: 3 years Mean survival time: 55 months Mean disease-free survival time: 49 months		
		3 years	5 years
	Overall survival:	82%	77%
	Disease-free survival:	69%	59%
	TPI (treatment-dependent prognosis index) at 3 years of survival, 63%, and at 5 years, 56%		
Toxicity	Extremely low side effects only grade III		
Conclusions	Survival of patients treated with neoadjuvant IA chemotherapy was better than TPI		

Kovács (2005) [4]

Concept	Chemoembolization using cisplatin crystals as neoadjuvant treatment of oral cancer
N	103
Inclusion criteria	Histologically proven, previously untreated primary SCC of the oral cavity and anterior oropharynx T0–T4
Therapy	IA chemoembolization, 150–300 mg/m^2 highly concentrated aqueous suspension of cisplatin with precipitation of crystals; simultaneous IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s)
Results	Overall response after one procedure CR + PR = 73%, SD = 24%, PD = 3% (only T4) Pathological CR after one procedure: 18.5%
Toxicity	Post-embolization syndrome: leukocytosis, 62%; pain, 71%; swelling, 24% Acute toxicity: hypokalemia, 26%; hyperglycemia, 26%; hepatic enzymes, 12%; serum creatinine, 10%; nausea, bilirubin, LDH, serum ferrum, 7%; hyperuremia, 5%; no toxicity, 17%
Conclusions	Chemoembolization of cancer in the head and neck area can be carried out regularly and safely using this method and is highly effective

Robbins et al. (2005) [5]

Concept	High-dose IA cisplatin and concurrent radiation for head and neck carcinoma (multicenter prospectively) multi-RADPLAT			
N	61			
Inclusion criteria	Squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, or larynx stage IV, T4, N0–3, M0; Karnofsky performance score ≥60; age ≥18 years			
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 /3–5 min sodium thiosulfate followed by 12 g/m^2/6 h sodium thiosulfate (weekly for 4 weeks); concomitantly radiotherapy, 2 Gy per fraction once a day, 5 days a week; total dose of 66–74 Gy in 35 fractions during 7 weeks			
Results	CR = 85% at primary tumors and 88% at nodal regions; overall CR = 80%			
	Median follow-up: 3.9 years			
	Estimated	1 year (%)		2 years (%)
	Locoregional control	66		57
	Survival rate	72		63
	DFS	62		46
Toxicity	Parameter	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
	Hematologic	31	18	2
	Nonhematologic	56	23	3
	Mucosal	48	10	0
	CNS	7	2	0
	Infection	10	2	2
	Overall worst per pts	44	39	3
Conclusions	IA cisplatin with RT was feasible and effective in the multi-institutional setting			

Rasch et al. (2010) [6]

Concept	Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer (randomized phase 3 trial)
N	239
Inclusion criteria	Functionally unresectable head and neck cancer patients

Therapy	IA, 4 × 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2/15–20 min sodium thiosulfate followed by 12 g/m^2/6 h sodium thiosulfate (on days 1, 8, 15, 22); concomitantly radiotherapy, total dose of 70 Gy in 35 daily fractions IV, 3 × 100 mg/m^2 cisplatin (on days 1, 22, 43); with the same radiotherapeutic regimen			
Results	Median follow-up: 2.75 years			
	At 3 years	IA (%)	IV (%)	*p*-value
	Local control	76	70	0.61
	Locoregional control	63	65	0.72
	DFS	44	47	0.94
	Disease-spec. survival	69	71	0.57
	Distant metastasis FS	66	69	0.51
	Overall survival	51	47	0.41
Toxicity	Renal toxicity significant lower in the IA arm 1% vs. 9% Hematological toxicity > grade 2 was 52% IA vs. 42% IV Mucosal toxicity > grade 2 50% IA vs. 54%IV Ototoxicity >5 dB 53% IA vs. 58% IV Cardiac/pulmonary > grade 2 5 pts. IA vs. 9 pts. IV Neurological > grade 2 8 pts. IA vs. 1 pts. IV			
Conclusions	Cisplatin-based IA chemoradiation was not superior to intravenous chemoradiation for advanced stage IV head and neck cancer			

Mendenhall et al. (2010) [7]

Concept	Altered fractionation and adjuvant chemotherapy for head and neck squamous cell carcinoma (meta-analysis, review)
N	App. 10,000 (RT), app. 40,000 (adjuvant chemotherapy)
Inclusion criteria	Previously untreated patients with stage III–stage IVA and/or IVB HNSCCs (nonmetastatic)
Therapy	Hyperfractionated RT (HFRT) vs. accelerated fractionated RT (AFRT) compared with conventionally fractionated RT (CFRT); adjuvant chemotherapy

Results	1. HFRT is more efficacious than either CFRT or AFRT 2. Concomitant chemoradiation is more efficacious than RT alone 3. Concomitant chemotherapy is more effective than induction or maintenance chemotherapy 4. Intra-arterial chemotherapy is no more effective than intravenous chemotherapy 5. Monochemotherapy is as effective as polychemotherapy 6. The most effective chemotherapeutic agents are fluorouracil, cisplatin, and cetuximab 7. The role of induction chemotherapy followed by concomitant chemoradiation remains unproven
Conclusions	Altered fractionation and/or concomitant chemotherapy results in improved outcomes compared with conventionally fractionated definitive RT alone for stage III–stage IV HNSCCs. The optimal combination of RT fractionation and chemotherapy remains unclear

Nishio et al. (2011) [8]

Concept	Intra-arterial chemoradiation therapy for oropharyngeal carcinoma with high-dose cisplatin (retrospective study)
N	21
Inclusion criteria	Oropharyngeal carcinoma, stages II–IVB
Therapy	d1 and 35: 300 mg/m^2 (<70 years); 200 mg/m^2 (≥70 years) cisplatin IA d2-ff: radiation (2 Gy per day; max. 60 Gy) d1–4 and 8–11: 1000 mg/m^2 5-FU IV
Results	2-year overall survival: 71.3% 2-year locoregional control and disease-free survival rate: 95.0% and 67.7%

Toxicity	Mucositis (grade II): all patients except for one with grade III Hematological toxicity (grade III): one patient Dysphagia (grade III): one patient Nephrotoxicity: six patients (three had grade I and three had grade III) No intra-arterial-intervention-related complications
Conclusions	Selective intra-arterial high-dose cisplatin chemotherapy with concomitant radiation therapy is well tolerated. It can achieve good results in patients with oropharyngeal carcinoma

Takayama et al. (2016) [9]

Concept	Alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy (prospective study)
N	33
Inclusion criteria	Tongue cancer (stage III–IVB)
Therapy	d1–5: 700 mg/m^2 5-FU d6: 110 mg/m^2 nedaplatin Week 1–5: radiation (36 Gy in 20 fractions) Proton beam therapy 28.6–39.6 Gy in 13–18 fractions From week 7: 20–40 mg/m^2 cisplatin IA (weekly 4–6×)
Results	24 patients (72.7%) completed the course CR: 28 patients (84.8%) PR: 5 (15.2%) Median period to recurrence: 6 months (range 5–31) Relapse rate: 8 patients (2 at the primary site, 3 at the cervical lymph node, 1 at the primary site and the cervical lymph node, 1 at the primary site and distant metastasis, 1 at the cervical lymph node and distant metastasis) Three-year OS, PFS, LC, and RC rates: 87.0%, 74.1%, 86.6%, 83.9%

Toxicity	Major acute adverse events (>grade 3): mucositis in 26 (79%) patients, neutropenia in 17 (51%), and dermatitis in 11 (33%) Neutropenic sepsis (involving catheter-related infection): six patients (18%)
Conclusions	PBT-IACT for stage III–IVB tongue cancer has an acceptable toxicity profile and shows good treatment results. This protocol could be considered as a treatment option for locally advanced tongue cancer

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