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Selective intraarterial cisplatin chemotherapy in treatment of advanced malignant squamous cell carcinoma of the head and neck

Review Article

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Summary

The prognosis for patients with advanced head and neck cancer is poor and only a small fraction of these patients are cured. The standard therapy of advanced head and neck carcinomas consists of surgical resection of the tumor with postoperative radiation. Chemotherapy has been added to combined treatment modality of advanced head and neck cancer in attempts to improve survival rates. Selective injection of the cytostatic agents into the tumor-supplying artery is an attractive method to achieve higher doses of cytostatic agents in the tumor with less systemic toxicity and low complication rate. A combination of regional chemotherapy by intraarterial infusion of high doses of cisplatin with radiation therapy seems to be an useful approach when planning integrated treatment for locally advanced head and neck cancer.

I. Therapy of advanced carcinomas and its limits

Carcinomas of the upper aerodigestive tract detected in early stage have in general a good prognosis after surgical therapy or irradiation. However, this statement is not valid for advanced carcinomas of stage III and IV according to UICC which represent about two third of the carcinomas of this region.

The current results of therapy of advanced carcinomas of the upper aerodigestive tract can only be compared with significant restrictions as carcinomas in the stage III and IV may consist of tumors with different prognosis. However, these data demonstrate an average rate of locoregional recurrence of more than 50% and according to autopsy studies approximately 50% of these patients develop distant metastasis (Dennington et al, 1980). The five-year survival rate of advanced head and neck carcinomas rarely achieves more than 25% (Vokes et al, 1993; Hart et al, 1995).

The standard therapy of advanced head and neck carcinomas (stage III and IV) consists of surgical resection of the tumor in combination with radiotherapy. Chemotherapy has been added to combined treatment modality of advanced head and neck cancer in attempts to improve survival rates and for organ function preservation. Chemotherapy is performed in case of non-resectable tumors or in case of tumors of which resection would lead to an unacceptable functional loss and in case of tumors for which postoperative radiation therapy alone is unsatisfactory.

Cisplatin, 5-fluorouracil, and mitomycin C belong to the most effective chemotherapeutics in the treatment of squamous cell carcinomas of the head and neck. By combination with radiotherapy their radiosensitizing effects lead to a higher effectiveness of the therapy (Britzel et al, 1998). So often a slightly higher tumor control rate as well as survival rate could be achieved by application of simultaneous radiochemotherapy (Wendt et al, 1998; Pignon et al, 2000).

Antitumoral chemotherapy is generally applied systemically and transported through the blood circulation to all organs of the body. Thus other non-diseased organs are concerned beside the tumor. This could be accompanied by significant systemic side effects. The toxic effect to proliferating cells, as for example the bone marrow and the mucosa lead to a reduction of the chemotherapeutic dose. Applying a standard dose often results in a subtherapeutic intratumoral concentration of the chemotherapeutics which reduces the effectiveness of this therapy concept. Another problem with chemotherapy is the development of drug resistance. In vitro and in vivo studies were able to describe a rapid development of

resistances against cisplatin during treatment (Inoue et al, 1985; Andrews et al, 1990).

II. Concept of intraarterial chemotherapy

Due to the poor prognosis of patients suffering from advanced head and neck cancers and the often unsatisfactory results of standard therapies, there is an urgent need for new therapeutical strategies. Especially in the last years several new therapeutical procedures for advanced head and neck carcinomas were developed and applied which are not yet included in the generally accepted methods. These are immunotherapy, photodynamic therapy, gene therapy as well as selective intraarterial chemotherapy.

The investigations performed by Robbins and co-workers gave new impulses to intraarterial chemotherapy the oncologic results of which are very promising. Robbins interprets their results in that way that the intraarterial chemotherapy with cisplatin coupled with radiotherapy allow a long-term survival (Robbins et al, 1997; Kerber et al, 1998; Robbins et al, 1999a).

Already in 1950, Klopp et al. reported that a more important effectiveness of chemotherapeutics can be achieved by a higher concentration of the intraarterial application. The increased effectiveness of intraarterial chemotherapy is based on the possibility of applying an up to ten times higher dose of cisplatin in comparison to intravenous standard therapy. This procedure should be sufficient to overcome the cellular drug resistance of cisplatin that rapidly develops (von Hoff et al, 1986; Teicher et al, 1987). The intraarterial application of cisplatin allows a higher effectiveness of chemotherapy with lower systemic toxicity which can be even favored by an accompanying therapy with thiosulfates. Thiosulfates can develop a soluble complex without toxicity due to covalent binding with cisplatin (Howell and Taetle, 1980). A disappearance of the active drug due to neutralization in the plasma compartment acts functionally as an increase in clearance.

The particular effectiveness of the intraarterial application of chemotherapeutics is based on the first passing of the drug through the tumor site. When the chemotherapeutics have reached the venous circulation they have the same effect compared to systemic application. The relative advantage of the intraarterial chemotherapy in comparison to intravenous application depends on the plasma clearance of cisplatin which is increased by the neutralizing effect of thiosulfates. This is also inversely proportional to the plasma flow of the tumor (Campbell et al, 1983). A reduction of the plasma flow of the tumor can be achieved by a rapid application of the medicament as well as the application in small arteries.

In the context of this therapeutical type the condition of the vessels providing the tumour must be considered. The experience of the first years of application of intraarterial chemotherapy made clear that the initial tumor resection and irradiation significantly influences the vascular provision of the tumors. Thus a higher effect of the chemotherapeutics could be achieved in cases of application as initial therapy with no prior surgery or irradiation possible impairing the blood supply of the tumor (Steffens et al, 1980). First experiences with intraarterial chemotherapy demonstrated furthermore that an isolated intraarterial chemotherapy is associated with a high rate of local recurrences. It could be postulated that this therapy should be considered as a part of a whole therapeutical concept with surgery and radiotherapy (Kreidler and Petzel, 1983).

The higher effectiveness of intraarterial chemotherapy in comparison to systemic chemotherapy could already be shown by animal experimental studies (Harker and Stephens, 1992). In the following sections the treatment results of advanced head and neck carcinomas by application of intraarterial cisplatin chemotherapy will be discussed.

III. Administration of intraarterial chemotherapy and treatment results

The precondition for the mentioned effect of intraarterial chemotherapy is the targeted selective injection of the cytostatic agent into the tumor-supplying artery. This is performed by means of different, specifically developed catheter systems. The so-called bypass method consisted in creating by vascular surgery a directly subcutaneously located cervical vessel which can be identified easily and cannulated repeatedly. By this method the external carotid artery was prolonged end-to-end by an autogenic saphenal vein graft and anastomosed with the common carotid artery end-to-side more proximally (Scheel, 1981). Further implantable pump systems were inserted for the application of chemotherapeutics in the past (Backer et al, 1987). Nowadays frequently chemotherapy is applied via angiographically guided selective placement of microcatheters into the tumor-supplying artery by means of a transfemoral access which can be performed repeatedly without significant complications.

The intraarterial chemotherapy was performed initially with cisplatin (100-200 mg/m^2 per week) in combination with intravenous sodium thiosulfate (9 g/m^2 for 30 minutes, followed by 12 g/m^2) for a maximum of four cycles (Robbins et al, 1992, 1994a, 1994b, 1996a). Later a combination of the intraarterial cisplatin therapy with radiotherapy was performed. Via a Seldinger catheter high doses of cisplatin were applied intraarterially coupled with simultaneous intravenous neutralization with sodium thiosulfate. This treatment was repeated and completed by parallel radiotherapy which served to reduce the total duration of the therapy and at the same time to increase the toxicity to the tumor. Radiotherapy of the tumor and its lymphatic pathways was performed in a dose of 1.8 to 2.0 Gy per day in 35 fractions for seven to eight weeks (total dose, 68 to 70 Gy). The intraarterial cisplatin therapy was performed on the first, eighth, fifteenth, and 22nd day of irradiation. Cisplatin was applied selectively via a microcatheter into the tumor-supplying artery for three to five minutes. It was dissolved in 400 ml of a electrolyte solution and transfused in a dose of 150 mg/m^2 each. Simultaneously the intravenous infusion of 9 g/m^2 sodium thiosulfate was performed for 30 minutes, followed by 12

g/m^2 for two hours. Pretherapeutically an intravenous hydratation was made with two liters of electrolyte solution. Posttherapeutically again an intravenous hydratation was performed with one liter of electrolyte solution. Patients with a clinically staged N2 or N3 neck underwent selective neck dissection two months after the beginning of therapy (Robbins et al, 1999a).

In the data established by Robbins et al. (1999b) 83 patients with intraarterial chemotherapy and radiotherapy were treated according to the above mentioned pattern. The patients suffered from carcinomas of the oral cavity, the oropharynx, the hypopharynx, and the larynx. 72 (87%) of the patients had four cycles, 9 (11%) of the patients had three cycles and 2 (3%) of the patients had less than three cycles of cisplatin. After a follow-up period of 17 to 61 months (median 24 months) 76 of the patients allowed a statement on the response rate of the therapy. Referring to the primary tumor 70 patients (92%) showed a complete response, 5 patients (6%) revealed a partial response, and in one patient (1%) no response could be observed. Neck dissection was performed in 30 of 52 patients with N2 or N3 neck. Referring to the cervical lymph nodes, 64 patients (84%) had a complete response and 11 (14%) showed a partial response. Only one patient revealed a response neither in the area of the primary tumor nor in the cervical region. After a follow-up period of 30 months an average survival rate of 58% and a five-year survival rate of 40% could be observed.

In analogy to these results most of the applied therapeutical procedures with intraarterial chemotherapy combined with radiotherapy revealed an overall response rate of about 90%. These recent results are demonstrated in **Table 1**.

In an investigation on the effectiveness of intraarterial chemotherapy 45 patients suffering from T4 carcinoma with cartilage or bone infiltration were compared to 90 patients suffering from T4 carcinoma without cartilage or bone infiltration (Samant et al, 2001). The complete response rate of the first group amounted to 66.7% which reveals no significant difference to the second group with 71.1%. The two-year survival rate of both patient populations showed no significant difference (46.3% versus 36.9%).

The analysis of the quality of life after radiochemotherapy with intraarterial application of cisplatin showed an initial reduction of the quality of life for the patients with advanced oropharyngeal, hypopharyngeal, and laryngeal carcinomas. However, generally an amelioration of the quality of life could be confirmed after the end of the therapy and the values even exceeded the pretherapeutical number of points six months after the end of the therapy (Murry et al, 1998). In another investigation the quality of life of patients suffering from head and neck cancer of stage IV who were treated according to the above mentioned radio/ chemotherapeutical concept was analyzed. Appropriate questionnaires were evaluated prior to treatment as well as three, six, and twelve months after therapy (Ackerstaff et al, 2002). This evaluation also revealed that the quality of life deteriorated initially in order to improve between the third and twelfth month.

IV. Side effects of the intraarterial chemotherapy

Complications resulting from the application of the catheter which have to be treated and vascular complications during angiography and chemotherapy are relatively rare. In a study of 105 patients 385 transfemoral catheterization of the external carotid artery were performed. Gemmete (2003) reported about two asymptomatic dissections of the distal common carotid artery and 22 hematomas which did not need therapy as well as acutely arising occlusions in the area of the femoral and iliacal artery in three patients.

Because the tumor is specifically treated via an angiographical microcatheter in the context of this therapeutical concept the systemic side effects occur more rarely than in case of intravenous chemotherapy. Additionally the overlapping intravenous application of the cisplatin antagonist sodium thiosulfate neutralizes the systemic side effects. This therapy reduces the cytostatics-related nausea, especially when the maxillary artery and thus the arteria meningia media are not located in the area of transfusion. However, an antiemetic therapy is generally recommended. Renal insufficiencies can be sufficiently excluded by an accompanying intravenous hydratation (Robbins et al, 1996b).

During the 323 transfemoral selective intraarterial transfusions a severe chemotoxicity was observed in 5% of the cases. In nine cases this included severe gastrointestinal side effects, in seven cases severe hematological side effects, in one case even neurotoxicity and one death during therapy secondary to a pulmonary embolus. A serious ototoxicity or nephotoxicity did not occur. 25 (30%) of the patients developed a mucositis of degree III to VI. In six patients a neural dysfunction could be observed while three of these patients suffered from a cerebrovascular accident and three of them a transient ischaemic attack.

Table 1. Evaluable response rate referring to the advanced primary tumor for intraarterial chemotherapy combined with radiotherapy

author	number of patients	complete response	partial response	nonresponse
Samant et al, 1999	24	22 (88%)	1 (4%)	1 (4%)
Robbins et al, 1999b	76	70 (92%)	5 (6%)	1 (1%)
Fuwa et al, 2000	32	21 (66%)	10 (31%)	1 (3%)
Regine et al, 2000	20	18 (90%)	2 (10%)	0
Benazzo et al, 2000	40	11 (28%)	25 (63%)	4 (10%)
Samant et al, 2001	112	94 (84%)	15 (13%)	3 (3%)
Furutani et al, 2002	37	31 (84%)	4 (11%)	2 (5%)

Three patients developed pulmonary embolism while one patient died due to this pulmonary embolism, the other patients died after the end of the therapy due to aspiration pneumonia and/or coronary ischemia (Robbins et al, 1999b).

An analysis of swallowing and speech was performed of 14 patients suffering from head and neck cancer who were treated with intraarterial chemotherapy and irradiation in comparison to 16 patients treated with systemic radiochemotherapy. By means of videofluorography and articulation tests no significant difference could be found in comparison to the patients having undergone systemic radiochemotherapy one month after the end of the therapy (Newton et al, 2002). In another study 47 patients undergoing the same treatment were examined concerning the weight loss and swallowing prior to therapy and after the end of the treatment. These patients lost about 10% of their pretherapeutic weight and showed a reduction of the eating behavior. 18 months after the end of the therapy most of the patients were able to eat normally and to keep their weight. The percentage of patients without dysphagia sank during treatment from 38% (18 patients) to 21% (10 patients), and after 18 months after the end of the therapy it increased to 72% (34 patients). The complaints of dysphagia during therapy were in particular the result of mucositis and nausea. While prior to therapy 4 patients (9%) had a PEG tube 12 patients (26%) needed such a probe during treatment. After the end of the therapy up to 18 months afterwards the need of a PEG tube was reduced to 13% (6 patients) (Newman et al, 1998).

The ototoxicity of the intraarterial cisplatin therapy was examined in 70 patients (Madasu et al, 1997). The ototoxicity was defined as hearing loss of 15 dB for one frequency or 10 dB for three frequencies between 250 Hz and 4 kHz. The incidence of ototoxicity was 25% for 150 mg/m^2, 50% for 300 mg/m^2, 64% for 450 mg/m^2, and 60% for 600 mg/m^2. The ototoxicity could only be observed in the high frequencies. The hearing at 2 kHz and frequencies below 2 kHz were concerned only minimally or not affected. The ototoxicity occurred independently from an initially existing hearing loss. A vestibular lesion or tinnitus could not be observed.

V. Conclusion

The selective intraarterial chemotherapy can be included in the therapy of carcinomas where surgery and radiotherapy do not promise a curative treatment. Contraindications such as for example a tendency to bleeding against the performance of chemotherapy should not exist. Further a sufficient blood supply of the tumor should be revealed.

Intraarterial chemotherapy seems to be a promising strategy in therapy of untreated locally advanced head and neck cancer with concurrent radiotherapy due to advantages of high-dose delivery of drug, minimal procedural complications, low systemic toxicity, and high tumor response rate. Further clinical trials are required to fully assess the effect of intraarterial chemotherapy on survival rate and quality of life in treatment of advanced head and neck cancer.

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