

Results of combined modality treatment in patients with primary unresectable cancer of the oral cavity

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Aim. Neoadjuvant chemotherapy may improve the results of treatment for primarily unresectable cancer of the oral cavity. The aim of this study was to estimate the tolerance and early results of neoadjuvant chemotherapy followed by surgical resection of oral cavity cancer, with immediate reconstruction and adjuvant radiotherapy.

Material and method. 56 patients hospitalized at the Department of Head and Neck Cancer of the Maria Skłodowska-Curie Memorial Cancer Centre - Institute of Oncology between August 1997 and June 2000 were enrolled for the purpose of the study. When tumour regression was observed after 2-4 courses of neoadjuvant chemotherapy consisting of cisplatin, 5-fluorouracil, methotrexate, vinblastin, etoposide and leucovorin, the patients were referred for surgical resection with immediate reconstruction, followed by adjuvant radiotherapy.

Results. Regression of the primary tumor and lymph nodes of the neck was observed in 41 patients, all of whom were referred for radical surgery followed by adjuvant radiotherapy. The tolerance of combined treatment was acceptable. Complete regression was obtained in 37/56 patients. During observation 12 patients failed due to locoregional progression and 2 due to distant metastases. 23/56 patients (41%) are alive without evidence of disease.

Conclusions. Neoadjuvant chemotherapy allows for radical resection in a majority of patients with primarily unresectable cancer of the oral cavity. The tolerance of treatment is good. What is important, radiotherapy and chemotherapy do not impair wound healing and vascularity of musculo-cutaneous island flaps.

Wyniki skojarzonego leczenia chorych na pierwotnie nieoperacyjnego raka jamy ustnej

Zastosowanie indukcyjnej chemioterapii stanowi jedną z metod mogących poprawić wyniki leczenia w wybitnie źle rokującej grupie chorych na pierwotnie nieoperacyjne raki jamy ustnej.

Cel pracy. Ocena tolerancji i wczesnych wyników leczenia skojarzonego złożonego z indukcyjnej chemioterapii, szerokiej resekcji chirurgicznej z ew. jednoczesną rekonstrukcją oraz uzupełniającej radioterapii u chorych na pierwotnie nieoperacyjne raki jamy ustnej.

Metoda i materiał. Indukcyjna chemioterapia złożona była z cisplatyny, 5-fluorouracylu, metotreksatu, winblastyny, etopozynu i leukoworiny. Po 2-3 kursach leczenia, w przypadku uzyskania regresji raka, przeprowadzano zabieg operacyjny z jednoczesną rekonstrukcją, a następnie uzupełniającą radioterapię. W okresie od sierpnia 1997 do czerwca 2000 do leczenia zakwalifikowano 56 chorych.

Wyniki. W efekcie indukcyjnej chemioterapii u 41 chorych uzyskano regresję nowotworu umożliwiającą przeprowadzenie zabiegu operacyjnego. Wszyscy chorzy po leczeniu operacyjnym zostali zakwalifikowani do uzupełniającej radioterapii. Tolerancja chemioterapii i radioterapii była zadowalająca. Nie obserwowano również istotnych powikłań w przebiegu pooperacyjnym. W szczególności nie stwierdzono negatywnego wpływu leczenia chemicznego i napromieniania na gojenie i adaptację unaczynionych płatów skórno – mięśniowych używanych przy rekonstrukcji. U 4 chorych stwierdzono progresję w trakcie uzupełniającej radioterapii. Całkowitą regresję nowotworu po zakończeniu leczenia stwierdzono u 37/56 chorych (66%). W trakcie obserwacji progresja nowotworu wystąpiła u 14 chorych; w tym u 12 nawrót miejscowy zaś u 2 przerzuty odległe. Obecnie żyje bez cech nawrotu 23/56 pacjentów (41%).

Wnioski. indukcyjna chemioterapia pozwoliła na przeprowadzenie radykalnego zabiegu chirurgicznego u większości chorych na pierwotnie nieoperacyjnego raka jamy ustnej. Tolerancja leczenia była dobra, a w szczególności proces gojenia i adapta-

cji odległych, unaczynionych płatów skórno-mięśniowych u chorych poddanych chemio- i radioterapii, przebiegał prawidłowo.

Key words: oral cavity cancer, combined modality treatment, neoadjuvant chemotherapy, immediate reconstruction
Słowa kluczowe: rak jamy ustnej, leczenie skojarzone, indukcyjna chemioterapia, natychmiastowa rekonstrukcja

Introduction

Hemiglossectomy or oral cavity floor resection combined with radical or modified radical dissection of neck lymph nodes is the treatment of choice in patients with locally advanced cancer of the oral cavity. In more advanced cases the range of resection may be extended by hemimandibulectomy or partial resection of the mandibula combined with reconstruction. Surgery is often followed by adjuvant radiotherapy, usually dependant on the results of histopathological examination. Patients not suitable for resection due to locally advanced present with a highly unfavourable prognosis. Despite unsatisfactory results, irradiation is the only alternative to radical surgery. Some hope lies in unconventionally fractionated radiotherapy or simultaneous irradiation and chemotherapy. Patients with cancer infiltration of the mandibula (a contraindication for irradiation) cannot be qualified for radical treatment.

For many years attempts have been made to establish effective programs of neoadjuvant chemotherapy, followed by radical surgery or irradiation. Previous experiences have not allowed for any conclusive designs of combined treatment schedules, which could be recommended for routine use [1-3]. Despite negative results of clinical trials, neoadjuvant chemotherapy has preceded final regional treatment in American centers, is the most frequently applied combined modality scheme and still retains popularity [4-6]. Since August 1997 at the Department of Head and Neck Cancer of the Maria Skłodowska-Curie Memorial Cancer Center – Institute of Oncology in Warsaw a study was held in order to estimate the tolerance and efficacy of combined treatment consisting of neoadjuvant chemotherapy, wide resection & immediate reconstruction and adjuvant radiotherapy in patients with primarily unresectable cancer of the oral cavity.

Method

Inclusion criteria:

- squamous cell cancer of oral cavity, histopathologically verified in a biopsy specimen,
- diagnosis of primarily unresectable cancer – resection within safe margins impossible,
- exclusion of infiltration of internal and common carotid artery,
- performance status WHO 0-1,
- age <70,
- no distant metastases,
- no medical contraindications for chemotherapy with cisplatin and 5-fluorouracil.

Diagnostics:

- assessment of regional cancer progression (physical examination, histopathological verification of primary lesion and neck lymph nodes, neck sonography and possible mandibula panthomogram or CT scan),

- exclusion of distant metastases (chest X-ray, abdominal sonography),
- assessment of general condition.

Treatment began with chemotherapy consisting of cisplatin (30 mg/m² iv. days 2,3), 5-fluorouracil (300 mg/m² iv day 1), methotrexate (20 mg/m² iv day 1), vinblastine (3 mg/m² iv day 1) and etoposide (100 mg/m² iv days 2-3). Two to four courses were applied within 21 days. The number of courses depended on cancer regression allowing for resection.

In case of regression patients underwent radical surgery. In case of lack of regression, radiotherapy or symptomatic treatment (in patients with diagnosed infiltration of the mandibula) was applied.

Surgery consisted of wide tumor resection followed by reconstruction with pectoralis major myocutaneous island flap or free radial forearm flap. Additionally, unilateral radical or modified radical neck dissection was performed. Stage N2c patients were qualified for bilateral neck dissection: radical on the side of more advanced lesions, modified contralaterally.

Two to six weeks after radical surgery we started adjuvant radiotherapy. The irradiated volume consisted of the anatomical border of oral cavity and neck lymphatic system (entire in case of pN+, upper and middle part in case of pN-). Radiotherapy was performed with the use of conventional fractionation 2 Gy daily 5 times a week up to a total dose of 60 Gy. At the dose of 44 Gy a protective shield was used over the spinal cord, while the dose to posterior lymphatic nodes of the neck was increased with the use of electrons. The selective dose to the lower part of the neck lymphatic nodes and to the supraclavicular lymphatic nodes amounted to 50 Gy.

Chemotherapy toxicity according to the CTC scale (common toxicity criteria) was estimated before each course. Acute radiation reactions were evaluated according to the 5-grade EORTC/RTOG classification scale at least once a week throughout irradiation.

Follow up was performed once a month during the first 6 months after treatment, bi-monthly during the next 6 months and then every three months.

Material

Between August 1997 and June 2000 56 patients (13 women; 43 men) aged between 26-69 years (average: 52 years) were enrolled into the study.

The patients' clinical characteristic is shown in Table I. Performance status WHO 0 was observed in 27 patients, WHO 1 – in 29.

Moderately differentiated squamous cell carcinoma was the most frequent malignancy, being observed in 32 patients. Squamous cell carcinoma with poor differentiation was observed in 16 patients. Well-differentiated squamous cell carcinoma was observed in 8 patients. T3-T4 tumour progression was observed in all cases. During qualification only in 15 patients no lymph node metastases were observed. N1 metastases were observed in 17 cases, N2 in 17 and N3 in 7 cases.

Infiltration of both tongue and oral floor of the mouth was observed in most of the patients (34/56). Tumor limited to tongue or floor of the mouth was observed in 6 and 5 cases, respectively. In 11 patients the cancer was located in the alveolar process of the mandibula or in the retromolar triangle.

Clinical signs of infiltration of the mandibula or periosteum were observed in 39 patients.

Table 1. Patients' clinical characteristics

Number of patients	56
Age	26-69 years (median 52 years)
Women	13
Men	43
WHO performance status	
0	27
1	29
Cancer differentiation	
high differentiation G1	8
moderate differentiation G2	32
poor differentiation G3	16
Stage – T	
T3	15
T4	41
Stage – N	
N0	15
N1	17
N2	17
N3	7
Location of primary tumor	
tongue	6
floor of the mouth	5
tongue + floor of the mouth	34
mandibula alveolar processus/ /retromolar triangle	11

Results

Fourteen patients received 2 courses of chemotherapy, 17 patients – 3 and 25 patients – 4 courses.

Chemotherapy toxicity was evaluated according to the CTC scale. Neutropenia G1 was observed in 23 patients, G2 – in 6 cases. Neutropenia did not influence the dose and continuity of treatment in all patients, except in 3 cases, when it was necessary to delay one infusion. Thrombocytopenia and anemia, secondary to chemotherapy, were not observed. Mild and transient infections without influence on the continuity of therapy were observed in 8 patients. Nausea G1 according to CTC was observed in 16 patients. No chemotherapy-induced nausea was observed. No other side effects of chemotherapy were observed.

Regression of cancer allowing for radical surgery was observed in 41/56 patients. All of them were qualified for radical surgery. Partial resection of the tongue and floor of the mouth, and radical resection of the neck lymph nodes & reconstruction with neighboring tissues was performed in 7 patients. 33 patients also underwent hemimandibulectomy or partial resection of the mandibula, followed by reconstruction with the use of displaced, vascularized musculo-cutaneous flaps from the pectoralis major muscle. In one case, following resection of the anterior part of the oral cavity floor and partial resection of the mandibula, a musculo-cutaneous flap from the forearm (Chinese flap), was used for microsurgical reconstruction.

Satisfactory adaptation of displaced flaps, free of post-operative complications was observed in 37/41 cases.

Fistula was observed in one patient, successfully treated with conservative therapy. The fistula caused some delay in adjuvant irradiation, which duly began 8 weeks after the operation. Abscess within the flap peduncle, successfully treated with antibiotics, was another observed side effect. This complication did not influence the onset of adjuvant irradiation. Minor partial necrosis of the flap was observed in two cases, and also successfully treated with conservative therapy. The onset of radiotherapy was delayed in these two cases (9 and 10 weeks).

Histopathological examination proved locally complete excision of cancer in 35/41 cases. Infiltration of cancer was observed in the direct neighborhood of incision (0,1 mm) in 6 cases.

Significant chemotherapy-induced damage of cancer cells was observed in 18/41 cases. In 7/41 differentiation of cancer texture in tissues collected during the operation was higher than in the primary collected tissues. It could suggest chemotherapy-induced elimination of poorly differentiated cell clones. Complete patomorphological regression was observed in one patient.

All patients were qualified for adjuvant radiotherapy. During radiotherapy progression was observed in 4 cases. Progression in the upper part of the lymphatic system of the neck was observed in 3 cases, in one of these cases contralaterally to the primary lesions. This patient was qualified for modified neck dissection with the preservation of the internal jugular vein. In another case deep cervical lymph node progression occurred at the end of irradiation. Due to internal carotid artery infiltration the patient was not qualified for radical surgery. In this case, due to the occurrence of a fistula in the postoperative period, radiotherapy was started 8 weeks after the treatment. Bilateral progression in lymph nodes was also observed in the third patient, who was not qualified for salvage surgery.

Progression within the base of the tongue and the lateral part of the pharynx was observed in a single patient. He was not suitable for salvage surgery.

The remaining patients completed irradiation in the planned dose and without progression. Acute cutaneous and mucosal reactions were observed in 5 patients in G1, 21 in G2, 15 in G3.

Acute radiation reactions caused unscheduled delays in irradiation in 9/41 patients.

The delays lasted from 4 to 15 days. In one case two delays, each of 7 days, were necessary. The intensification of the acute radiation reaction in the displaced musculo-cutaneous flaps was similar to that observed in the neighboring tissues. No blood supply disorders and final adaptation disorders of displaced musculo-cutaneous flaps were observed during irradiation and follow-up.

Complete regression was obtained in 37/56 patients (66%) – i.e. all who had completed adjuvant irradiation according to the designed dose. During observation (ranging between 6 and 40 months; median – 17 months) cancer progression was observed in 14/37 patients after complete regression. Recurrence within primary lesion and/or neck lymph nodes was the site of progression in 12 pa-

tients. Distant metastases to lungs and liver were observed in two cases. 28 patients died during follow-up. Progression of cancer was the cause of death in 27 cases. One patient died from unrelated causes.

At present 23/56 (41%) patients are alive and disease-free. The survival time in this group ranges from 6+ to 37+ months (average: 15+ months).

Discussion

For a number of years clinical trials have been conducted to estimate the results of chemotherapy, followed by radical surgery or irradiation, in patients with advanced cancer of the head and neck. Such sequence of combined treatment before surgery is designed to reduce the tumor mass and render operation possible. The reduction of tumor mass brought on by chemotherapy, followed by irradiation, enables the application of radical radiotherapy and may improve vascularization of the tumour, thus further increasing the efficacy of radiation. In both cases chemotherapy consistent with spatial interaction, reduces the possibility of treatment failure by eliminating subclinical, distant metastases.

Chemotherapy followed by irradiation arouses theoretical controversies, including the extension of treatment time, the intensification of repopulation during radiotherapy and the risk of evolving cell clones resistant to cytostatics which could also be resistant to irradiation [2]. Chemotherapy probably influences tumor biology and the "normal" clinical course of disease in patients undergoing surgery. If lesion removal is incomplete there is a high risk of an intense repopulation by the remaining cancer cells. This has negative influence on the efficacy of irradiation following radical surgery. As it has already been stressed there is also the risk that cancer cells resistant to chemotherapeutic drugs could be resistant to radiotherapy [6]. Previous clinical trials have presented similar results. Chemotherapy results lead to cancer regression in some 60-90% patients [7-10]. On the other hand in a majority of randomized clinical phase III trials no influence of neoadjuvant chemotherapy was observed on the overall survival rate and disease-free survival rate [1, 7, 11-15]. Apart from the above-mentioned subtotal resections, spectacular tumour regression also had a negative influence on outcomes. In many trials no importance was attached to delays between treatment phases [6]. The delay between the termination of chemotherapy, resection and adjuvant irradiation may consequently significantly influence the final results of combined treatment [6].

The presented treatment program refers to a selected group of patients suffering from cancer of the oral cavity primarily not qualified for resection. The chemotherapeutic drugs listed in the protocol have mutual synergic activity; the expected toxicity is low, thus allowing for immediate radical surgery. Chemotherapy tolerance was good. Side effects did not have a significant influence on the continuity of treatment in the pre-designed doses, as well as on the time of surgery.

Radical surgery is the most critical element of treatment. Extensive resections within the oral cavity, especially combined with hemimandibulectomy or partial resection of the mandibula, make reconstruction necessary. In such cases vascularized musculo-cutaneous flaps from the pectoralis major muscle are most popular. Their reliability is unquestioned in patients who did not undergo radiotherapy or chemotherapy. Our study has shown that both neoadjuvant chemotherapy and adjuvant irradiation have no negative influence on the vascularization of displaced flaps and thus also on the final effects of reconstruction.

Similarly, though only in a sole case, no influence of chemotherapy or radiotherapy was observed on the adaptation of a free microvascularly anastomosed musculo-cutaneous flap.

The postoperative period was uneventful in 37/41 cases. Wound healing and adaptation of flaps was normal. The tolerance of adjuvant irradiation was satisfactory. Acute radiation reaction was similar within the distant flaps and the neighboring tissues.

No radiotherapy-induced complications were observed within the reconstructed site.

Early outcomes of combined therapy appear satisfactory, although it should be emphasized that the observation period is still relatively short. Only patients with advanced local cancer were eligible for the study. In a majority of cases at the onset the patients were beyond radical treatment due to mandibular infiltration. Therefore it appears justifiable to apply the presented treatment program in this particular group of patients.

Conclusions

1. Induction chemotherapy allows to perform radical surgery in a majority of patients with primarily unresectable cancer of the oral cavity.
2. Tolerance of combined treatment (including chemotherapy, radical surgery and radiotherapy) was satisfactory in patients with advanced cancer of the oral cavity.
3. Radiotherapy adjuvant to induction chemotherapy and radical surgery does not influence the vascularization and adaptation of vascularized musculo-cutaneous flaps from the greater pectoral muscle or free flaps with microvascular anastomosis used for the reconstruction of excised tissues.

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