

Induction Chemotherapy with Docetaxel, Cisplatin and 5-fluorouracil for Tongue Cancer

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Induction chemotherapy consisting of one cycle of docetaxel, cisplatin and 5-fluorouracil (5-FU) was evaluated for its primary effects on squamous cell carcinoma of the tongue. The patients were five men and one woman, 50 to 67 (mean 57.8) years of age. Clinical staging of the tongue cancers showed two patients with stage III and four with stage IV disease. All patients underwent one cycle of intravenous chemotherapy with docetaxel (60 mg/m², on day 1), cisplatin (10 mg/m², from days 1 to 5) and 5-FU (500 mg/body, from days 1 to 5) before surgical operation. The overall response rate was 83.3% (five PRs and one NC), with two cases with grade II A in the Ohboshi & Shimosato classification and four with grade II B. The main side effect was severe neutropenia, which was effectively managed with granulocyte colony-stimulating factor (G-CSF).

In conclusion, induction chemotherapy with docetaxel, cisplatin and 5-FU for tongue cancer was tolerated well by all the patients and showed an excellent response rate in spite of only one cycle of administration.

Although patients with oral cancer in the early stages (I and II) are often cured by radiotherapy or surgery alone, patients in more advanced stages (III and IV) frequently require a multimodality approach to obtain satisfactory results. Cisplatin and continuous infusion of 5-fluorouracil (5-FU) have been established as the standard induction regimen for advanced cases [1,2]. For head and neck cancers, this regimen has produced response rates of 60-90% and complete response (CR) rates of 20-50% [1,3,4].

Docetaxel is an effective agent which when used alone, has produced response rates of 21-42% for patients with locally advanced, recurrent, and/or metastatic disease [5,6,7]. Docetaxel differs in its mechanism of action from cisplatin and 5-FU. Therefore, some investigators have examined combining these agents to achieve better response and cure rates. Thus, we also examined an induction chemotherapy regimen consisting of docetaxel, cisplatin and 5-FU in one cycle of administration for the treatment of advanced squamous cell carcinoma of the tongue, a major oral cancer.

PATIENTS AND METHODS

This study included six patients with untreated squamous cell carcinoma of the tongue who were treated between December 2001 and March 2003 (Table I). The patients comprised five men and one woman, 50 to 67 (mean 57.8) years of age. Two patients had

Table I.

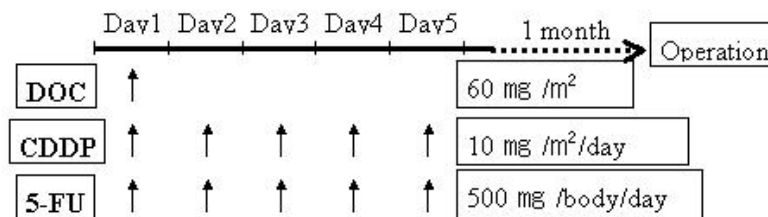
Case	Age (years)	Sex	Histologic differentiation	TNM	Stage	Side effects (Grade)	Dose/Times of G-CSF	Response	Ohboshi & Shimozato classification
1	67	M	well	T3N0 M0	III	L(IV),N(III),T(III)	100 μ g/13	PR	II B
2	50	M	well	T3N2cM0	IVA	N(III),A(III),D(III)	100 μ g/3	PR	II B
3	60	M	moderately	T4N2bM0	IVA	L(III),A(III)	75 μ g/3	NC	II A
4	54	F	well	T3N1 M0	III	L(III),N(III),A(III)	100 μ g/5	PR	II A
5	55	M	moderately	T4N2cM0	IVA	N(III),A(III)	100 μ g/3	PR	II B
6	61	M	moderately	T1N2cM0	IVA	A(III)	100 μ g/5	PR	II B

L=Leukopenia, N=Neutropenia, T=Thrombocytopenia, A=Alopecia, D=Diarrhoea (NCI-CTC Version 2.0)

stage III and four had stage IV disease. The performance status (ECOG) of all patients was less than II. The study protocol was approved by our Institutional Review Board, and all patients went through an informed consent process.

All patients received one cycle of intravenous chemotherapy with docetaxel (60 mg/m², on day 1 for 1 hour), cisplatin (10 mg/m², from days 1 to 5, for two hours) and 5-FU (500 mg/body, from days 1 to 5, continuous infusion) as the induction treatment (Table II). Side effects were assessed in accordance with “Common Toxicity Criteria v. 2.0” [8]. One month

Table II. Schedule of Emotherapy



after the start of chemotherapy, clinical responses were assessed by inspection, palpation and CT-scan or magnetic resonance imaging (MRI). The *tumor regression rate* was defined as the percentage reduction achieved in the cross-sectional area of a measurable tumor through use of the product of the 2 largest perpendicular diameters and the following formula:

$$\text{Tumor regression rate (\%)} = (1 - \text{tumor size after preoperative therapy} / \text{pretreatment tumor size}) \times 100.$$

Disappearance of all known disease due to the chemotherapy was evaluated as a complete response (CR). A partial response (PR) was defined as a *tumor regression rate* of at least 50%, while no change (NC) was less than 50% or more than -25%.

This assessment was followed by radical surgery, and the histological effects were evaluated based on Ohboshi & Shimozato classification [9] using the surgical specimens.

RESULTS

The results are presented in Table I. The overall response rate with this regimen was 83.3%. CR was not observed, but PR was obtained in five cases. Only one patient was evaluated as NC, whose primary lesion was located at the rear of the dorsal tongue. This patient died 6 months after the radical surgery. The histological assessment of all cases showed destruction of tumor structures as a result of the chemotherapy. In four cases, there was severe destruction and a few viable tumor cells that were assessed as grade II B

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according to the Ohboshi & Shimosato classification. On the other hand, the remaining two cases, including the one NC, were assessed as grade II A because destruction was incomplete and many viable tumor cells were observed.

Severe side effects of more than grade III were leukopenia, neutropenia, thrombocytopenia, alopecia and diarrhea. Alopecia occurred in five cases a few weeks after the start of chemotherapy. The nadirs of leukopenia (three cases) and neutropenia (four cases) were observed between days 6 and 10 but were manageable with granulocyte colony-stimulating factor (G-CSF). Thrombocytopenia and diarrhea were observed in only one case each. As mild side effects of less than grade III, nausea (three cases), and vomiting, stomatitis and dizziness (one case each) were also found.

Case 1

Case 1 was a 67-year-old male with left tongue cancer (T3N0M0). After one cycle of the induction chemotherapy, a marked response was observed and the *tumor regression rate* was determined at 60% by palpation, resulting in an assessment of PR (Figs.1 and 2). The patient underwent left radical neck dissection and a hemiglossectomy reconstructed with a rectus abdominis myocutaneous flap. The histological effect was evaluated as II B (Fig.3).

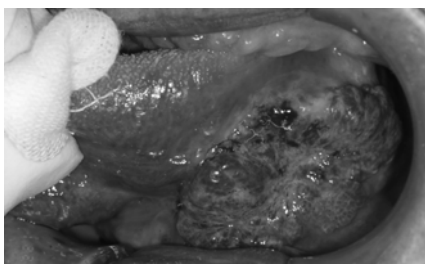


Fig.1. Left tongue cancer of case 1 before chemotherapy (T3N0M0).

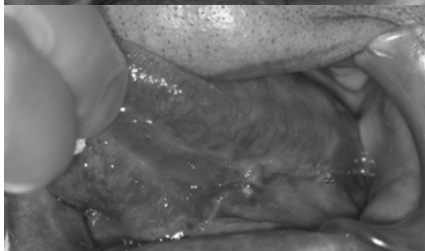


Fig.2. Left tongue cancer after one cycle of induction chemotherapy of case 1. Clinical response is assessed as PR.

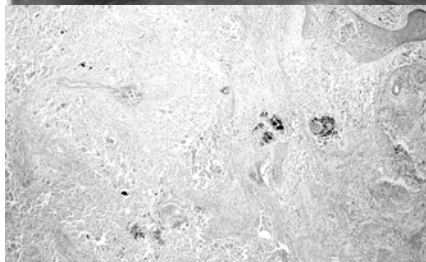


Fig.3. Histological findings of case 1 after chemotherapy. Tumor structures are destroyed severely and only a few viable tumor cells are observed. These findings are assessed as grade II B according to the Ohboshi & Shimosato classification.

Case 2

Case 2 was a 50-year-old male with left tongue cancer (T4N2cM0). After one cycle of the induction chemotherapy, marked response was observed but evaluation by palpation was difficult. MRI showed a *tumor regression rate* of 51% that was evaluated as PR (Figs.4 and 5). The patient underwent bilateral radical neck dissection and an almost total glossectomy reconstructed with a rectus abdominis myocutaneous flap. The histological effect was evaluated as II B (Fig.6).

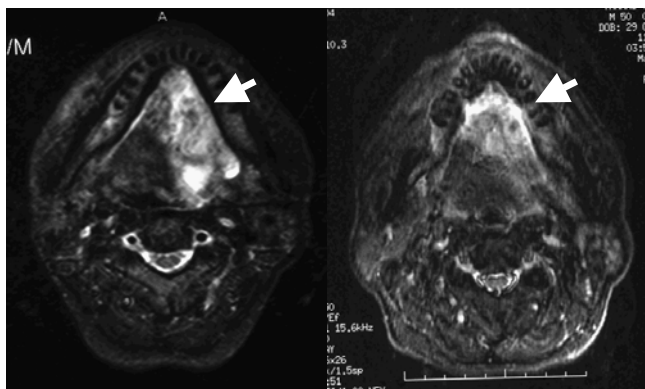


Fig.4.

Fig.5.

Fig.4. Magnetic resonance imaging (MRI) before chemotherapy of case 2. Arrow indicates left tongue cancer (T4N2cM0).

Fig.5. This MRI reveals tumor regression of case 2 after chemotherapy (arrow). Clinical response is evaluated as PR.

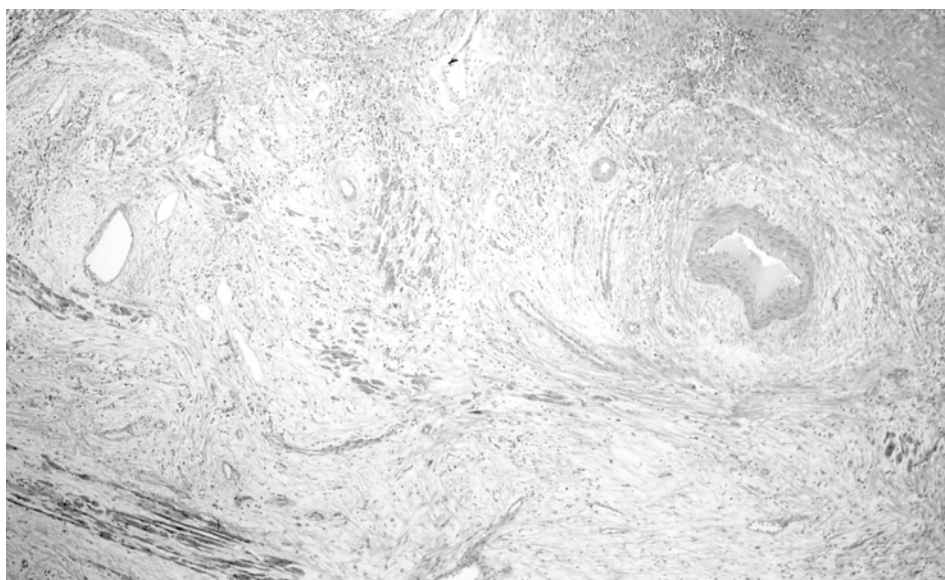


Fig.6. Histological findings of case 2 after chemotherapy. There is severe destruction of tumor structures with only a few viable tumor cells remaining that is assessed as grade II B.

Case 3

Case 3 was a 60-year-old male with right tongue cancer (T4N2bM0). After one cycle of the induction chemotherapy, marked response was observed but since the tumor was not palpable because the primary site was located at the back side of the dorsal tongue, the effect was evaluated as NC by means of MRI and CT (Figs.7 and 8). The patient underwent bilateral radical neck dissection as well as hemiglossectomy and hemimandibulectomy reconstructed with a pectoralis major myocutaneous flap, but he died after 6 months. The histological effect was evaluated as II A (Fig.9).

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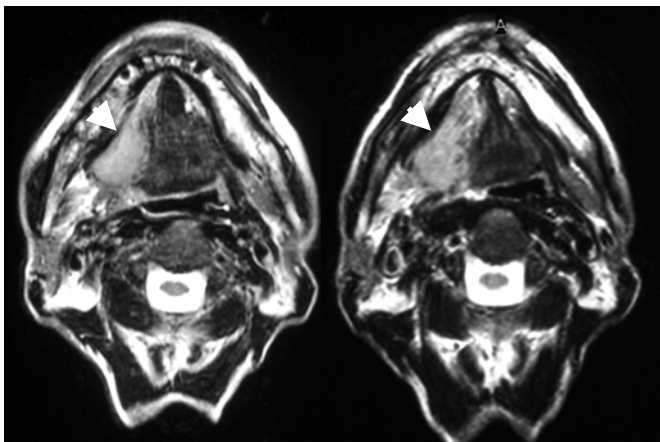


Fig.7.

Fig.8.

Fig.7. MRI before chemotherapy of case 3. Arrow indicates right tongue cancer (T4N2bM0).

Fig.8. MRI after chemotherapy of case 3. Tumor reduction can not be found by this image and it is evaluated as NC (arrow).

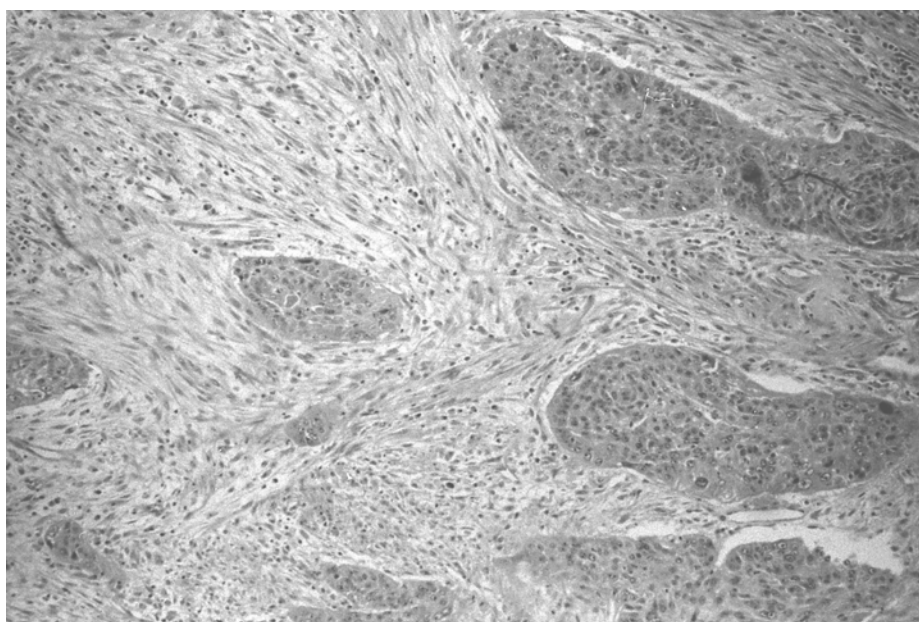


Fig.9. Histological findings of case 3 after chemotherapy. Tumor structures are destroyed mildly and many viable tumor cells are observed. These findings are assessed as grade II A.

DISCUSSION

One of the outstanding characteristics of docetaxel is expression of cytotoxicity for cisplatin-resistant cancers [10]. Therefore, combination chemotherapy comprising docetaxel and cisplatin has recently been tested. For locally advanced cancers of the head and neck, the combination chemotherapy of docetaxel and cisplatin resulted in a response rate of 53% [11]. This is inferior to the rates achieved with the standard induction regimen of cisplatin and 5-FU [1,3,4]. On the contrary, docetaxel, cisplatin and 5-FU in all combinations have produced response rates of 90-93% [12,13,14]. In those previous studies, the number of administered cycles of chemotherapy was more than three, and the target diseases were head

and neck cancers. On the other hand, in this study the number of administered cycles was decided as only one in order to decrease the total toxicity and reduce the period until radical surgery. Moreover, we restricted the target disease to tongue carcinoma, because the biological properties of head and neck cancers are not uniform due to regional peculiarities. In order to further reduce the toxicity, the administration of cisplatin in this study was done over a period of 5 days, with docetaxel preceding cisplatin [15,16].

Despite only one cycle of therapy, the overall response rate in this study was 83.3%. The tumors were able to be excised more safely, and functional oral organs were occasionally able to be preserved because of the tumor size reduction. Kirita *et al.* reported that residual tumor cells after preoperative therapy were found by microscopy in the deep tissue where there had been no clinical preoperative evidence of tumor invasion [17,18]. Their finding warns us to excise more carefully at the deep margins of tumors. With regard to the time interval between chemotherapy and surgery, the operation should not be delayed more than 5 weeks after the start of chemotherapy, since in this study the tumor size decreased greatly during the first 3 weeks but tended to increase thereafter. Although the one patient with NC had a poor outcome, there had been no apparent differences between the NC case and PR cases except for the primary location on the tongue, indicating that it is difficult to estimate the response before chemotherapy.

As for toxicity, side effects of more than grade III, consisted of leukopenia, neutropenia, thrombocytopenia, alopecia and diarrhea, but all were able to be cured. Alopecia and leukopenia or neutropenia were the most frequent, occurring in five patients (83.3%). Janinis *et al.* and Posner *et al.* also reported severe neutropenia following the same regimen, but also without any treatment-related deaths [12,13]. There were no instances of nausea, vomiting or renal failure of more than grade III in this study.

In conclusion, one-cycle induction chemotherapy with docetaxel, cisplatin and 5-FU for tongue cancer was tolerated well and yielded an excellent response rate. Since the survival rate could not be determined because the follow-up was less than 24 months, further long-term observations are required for a full assessment of the benefits and possible drawbacks of this regimen.

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