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Correlation Between Response to Induction Chemotherapy and Subsequent Radiotherapy in Previously Untreated Patients with Squamous Cell Carcinomas of the Head and Neck

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To determine the correlation between the response to induction chemotherapy and subsequent radiotherapy we analyzed the clinical records of 60 patients with locally advanced carcinoma of the head and neck retrospectively who had completed a full course (2~3 cycle) of induction chemotherapy and curative radiotherapy in Korea Cancer Center Hospital between 1986 and 1989. Chemotherapy was administeredd with CDDP+Bleomycin (BP) in 20, CDDP+5-FU (FP) in 37, and hybrid of BP and FP in three patients. Radiotherapy was given conventionally with a dose of 65 to 75 Gy or more over seven to eight weeks according to the size of lesion. Response rates following induction chemotherapy were 80% for the tumors and 79% for the nodes whereas complete reponse rates were 12% and 13%, respectively. Six months after radiotherapy 67% of the tumors and 77% of the nodes achieved a complete response. Among the 48 tumor responders and the 31 nodal responders to chemotherapy,39 (81%) and 28 (90%), respectively, achieved complete response after radiotherapy. Thus, whether or not the tumor and node respond to induction chemotherapy was predictive of the response to subsequent radiotherapy ($p<0.0005$ in tumor, $p<0.0001$ in node). By reanalyzing according to disease subsets (i.e. primary site, T-stage, N-stage) this relationship was not observed at T1-T2 disease ($p>0.3$). Therefore the tumor or node's response to induction chemotherapy is a predictor for subsequent radiotherapy except in T1-T2 tumors, and complete response to radiotherapy can be expected despite the failure of induction chemotherapy in T_1-T_2 tumors.

Key Words: Squamous cell carcinoma, Head and neck, Induction chemotherapy, Radiotherapy, Response to treatment, Correlation

INTRODUCTION

The theoretical and potential efficacy of the use of chemotherapy before surgery or radiotherapy (so-called induction chemotherapy, debulking, or neo-adjuvant chemotherapy) has been advocated since the early 1970s, and cis-platinum (CDDP)-based combination chemotherapy has been widely employed since the late 1970s especially in patients with locally advanced carcinomas of head and neck. At Korea Cancer Center Hospital, initial induction chemotherapy has been integrated since the early 1980s in the management of patients with locally advanced carcinomas of the head and neck. Early-on during these trials it was observed that patients who initially failed to respond to chemotherapy subsequently failed to respond to radiotherapy. Conversely, the responders to induction chemotherapy achieved an additional response to radiotherapy. Thus, the purpose of this study is as follows: first, to find out the correlation beween the response to induction chemotherapy and subsequent radiotherapy; second, to explore the possibility for using the response to induction chemotherapy as a predictive method for the response to subsequent radiotherapy in planned induction chemotherapy and radiotherapy; third, to explore the possibility for the using the response to induction chemotherapy as a tool for the modification of subsequent treatment method.

MATERIALS AND METHODS

Analyzing a relationship betweem response to induction chemotherapy and radiotherapy requires that patients have been treated with full courses of an effective chemotherapy followed by curative

radiotherapy and that responses have been fully evaluated after each treatment. In our institution induction chemotherapy has been employed on a full scale basis in locally advanced carcinomas of the head and neck since 1986 thus, data from 60 patients who were treated between 1986 and 1989 and met the qualifications were reviewed retrospectively. The stage of the disease was established according to the sytem of the American Joint Committee on Cancer of 1988[1]. These patients, pretreatment clinical characteristics are listed in Table 1. Chemotherapy (CT) was administered with 2 or 3 cycles of CDDP (100mg/m², dl)+Bleomycin (30u/d, d2 to d5) (BP) in 20, CDDP (100mg/m², dl)+5-FU (1g/m²/d, d1 to d5) (FP) in 37, and hybrid of BP and FP in 3 patients. Radiotherapy (RT) was given conventionally with a dose of 65 to 75Gy or more over seven to eight weeks according to the size of lesion with cobalt-60 teletherapy equipment.

Table 1. Pretreatment Characteristics of Patients (N=60)

Characteristics	No. of patients	(%)
Age (year)		
range	20 – 75	
median	49	
Sex		
male	48	(80)
female	12	(20)
Primary site		
oral cavity	3	(5)
paranasal sinus	8	(13)
nasopharynx	14	(23)
oropharynx	16	(27)
hypopharynx	15	(25)
larynx	4	(7)
T–stage		
T1	1	(2)
T2	20	(33)
T3	26	(43)
T4	13	(22)
N–stage		
N0	21	(35)
N1	5	(8)
N2 a	1	(2)
b	12	(20)
c	16	(27)
N3	5	(8)

Evaluation of response to chemotherapy was made three weeks after the end of the last course and that of radiotherapy was made three to six months after the end of radiotherapy. Statistical analysis was performed using the Log-rank test.

RESULTS

After induction chemotherapy, response rates (RR) were 80% for the tumors and 79% for the nodes, whereas, complete reponse (CR) rates were 12% and 13%, respectively. After radiotherapy, 67% of the tumors and 77% of the nodes achieved a complete response. To avoid bias in the study, patient population and results of treatment were tested at different levels before being analyzed. This preliminary step shows that in our population no difference can be displayed between results of the chemotherapeutic regimens ($0.2<p$) (Table 2), by T stage ($0.05<p$) (Table 3) or N stage ($0.975<p$) (Table 4).

Analysis of the evolution of the response to treatment from the end of chemotherapy to the sixth month after radiotherapy produces the follow-

Table 2. Response After Induction Chemotherapy According to Chemotherapy Regimens

	CR@	PR#	NR$	RR*	p-value
Bleomycin + CDDP (BP)	1	16	3	17/20 (85%)	
5–FU + CDDP (FP)	5	23	9	28/37 (76%)	$0.2<p$
BP/FP (hybrid)	1	2	0	3/3 (100%)	
Total	7	41	12	48/60 (80%)	

@CR : complete response # PR : partial response
$NR : no response *RR : response rate (CR+PR/CR+PR+NR)

Table 3. Response to Induction Chemotherapy According to T–stage

	CR	PR	NR	RR	p-value
T1	0	1	0	1/1 (100%)	
T2	3	14	3	17/20 (85%)	
T3	4	17	5	21/26 (81%)	$0.05<p$
T4	0	9	4	9/13 (69%)	
Total	7	41	12	48/60 (80%)	

Table 4. Response to Induction Chemotherapy According to N-stage

	CR	PR	NR	RR	p-value
N1	2	2	1	4/5 (80%)	
N2	3	20	6	23/29 (79%)	0.975<p
N3	0	4	1	4/5 (80%)	
Total	5	26	8	31/39 (79%)	

Table 5. Complete Response After Radiotherapy According to Response to Induction Chemotherapy

	Responders*	Non-responders	p-value
Primary tumor	39/48 (81%)	1/12 (8%)	p<0.0005
Node	28/31 (90%)	2/ 8 (25%)	p<0.001

* Responders : patients who had got CR or PR after chemotherapy

ing remarks:

1) Among the 48 tumor responders and the 31 nodal responders to chemotherapy, 39 (81%) and 28 (90%), resspectively, achieved complete response after radiotherapy.

2) Conversely, among the 12 tumor non-responders and the 8 nodal non-responders to chemotherapy, only one (8%) and two (25%), respectively, achieved complete response after radiotherapy. Thus, whether or not the tumor and node respond to incuction chemotherapy is predictive for the response to subsequent radiotherapy ($p<0.0005$ in tumor, $p<0.001$ in node) (Table 5).

This relationship was reanalyzed according to the tumor site, T-stage and N-stage. This was observed only at hypopharyngeal carcinoma ($p<0.005$) (Table 6), T3-T4 disease ($p<0.0005$) (Table 7), and N2 disease ($p<0.05$) (Table 8). It is thought that this relationship was not observed at the other primary site except in hypopharyngeal carcinoma and N1 and N3 disease due to the small number of patients in these groups for having statistical significances.

Therefore, the tumor or node responding to induction chemotherapy is predictive for subsequent radiotherapy except in T1-T2 tumor, and complete response to radiotherapy can be expected despite the failure of induction chemotherapy in T1-T2 tumor.

Table 6. Complete Response of Primary Tumor After Radiotherapy According to Response to Induction Chemotherapy and Tumor Site

	Responders	Non-responders	p-value
Oral cavity	1/1	0/2	0.6<p
Paranasal sinus	1/4	0/4	0.99<p
Nasopharynx	12/12	1/2	0.7<p
Oropharynx	11/15	0/1	0.3<p
Hypopharynx	10/12	0/3	p<0.05
Larynx	4/4	0/0	0.99<p

Table 7. Complete Response of Tumor After Radiotherapy According to Response to Induction Chemotherapy in T-Stage

	Responders	Non-responders	p-value
T1 + T2	15/18 (83%)	1/3 (33%)	0.3<p
T3 + T4	24/30 (80%)	0/9 (0%)	p<0.0005

Table 8. Complete Response of Node After Radiotherapy According to Response to Induction Chemotherapy in N-Stage

	Responders	Non-responders	p-value
N1	4/4 (100%)	0/1 (0%)	0.5<p
N2	20/23 (87%)	2/6 (33%)	p<0.05
N3	4/4 (100%)	0/1 (0%)	0.5<p

DISCUSSION

The use of combination of chemotherapy and radiotherapy has been based on the postulate that there is no cross-resistance between cytotoxic drugs and ionizing radiation. However, the correlation between the response to induction chemotherapy and subsequent radiotherapy has been suspected since the early trials of induction chemotherapy. This relationship can be found in an RTOG pilot study by Glick et al early in the literature[2]. But

it was Ensley et al that analyzed this relationship more systematically[3]. They studdied 57 untreated patients who underwent radiotherapy immediately after cis-platinum combination chemotherapy. Forty-one of the 42 responders (98%) subsequently responded to radiotherapy compared to 1 of the 18 nonresponders ($p<0.001$). The same observation has been reported in other studies[4~6] and is suggested in all those which conclude with better results for subsequent local treatment (surgery or radiotherapy) in responders than in nonresponders to induction chemotherapy[7]. However, most publications on induction chemotherapy in the head and neck have concerned locally advanced (Stage III and IV) diseases, and the correlation was suspected only in those disease subsets. Recently, Panis et al reported the relationship in an series of patients treated with induction chemotherapy, consisting of cis-platinum and etoposide[8]. They suggested a strong correlation with chemotherapy and radiotherapy responses in their advanced patients with T3 and T4, in contrast to T1 and T2 lesions, and noted that radiotherapy can be efficacious despite a failure of chemotherapy in Stage I and II patients. The results of our analysis were the same as Panix at al that is, even though chemoresistance is followed by radioresistance in bulky tumors, it does not occur in the early stages.

Early clinical experiences with the strong correlation of responses in advanced disease have led to in vitro studies making drug-resistant cell lines artificially[9~13]. Because ionizing radiation and a number of chemotherapeutic agents involve DNA damage as a common mechanism of action, the possibility of cross resistance is of at least theoretical importance. Belli and Harris[9] developed an adriamycin-resistant cell line by stepwise drug exposure to Chinese hamster lung fibroblast and observed the develpoment of a change in radiation response. Lourie et al[10] have developed a series of human ovarian cancer lines. They have obtained sublines resistant to adriamycin, melphalan, and cis-platinum. Cross-resistance to drug and radiation was observed in both the cis-platinum and melphalan resistant sublines; whereas, no cross-resistance was observed in the adriamycin resistant sublines. Wallner and Li[11,12] did not observe any increase in radioresistance in the Chinese hamster fibroblast cell lines made resistant to adriamycin and cis-platinum, respectively. Shimm et al[13] developed a subline from a human T-cell leukemia line by exposure to vinblastin, which showed a multidrug resistance associated with overexpression of P-glycoprotein. They observed a broader shoulder in cell survival curve by radiation. But this was not related to P-glycoprotein. By all accounts, drug resistance regardless of mechanism does not necessarily confer radiation resistance, Rather, a subpopulation of drug resistant cell lines might also demonstrate radiation resistance. Also, tumor microenvironment would lead to a cross-resistance.

Our study did not demonstrate any difference in response to chemotherapy between early and advanced diseases. This suggests that resistance to induction chemotherapy in head and neck carcinomas is essentially genetically induced and highest at the first onset. Conversely resistance to radiotherapy increases dramatically in bulky tumors. Origin of that can be found mainly in the surrounding factors. Indeed the size of the tumor and the consequent decrease of blood infusion in tumor tissue lead to cell hypoxia that is recognized as the main cause of failure in therapy by ionizing radiations. Thus, some tumors remain chemoresistant and become radioresistant by growing. Recently, the presence of radioresistant cell subline in tumors was advocated. Tumor cells can bear intrinsic radiorsistance which it may be consistent with tumor progression in large tumors. In rapidly growing tumors, possibly due to genetic instabliity, the likelihood of variant cell lines is the highest[14]. Thus, there might be common paramenters between the sensitivity and resistance to chemothrapy and radiotherapy. Clinical trial and basic reserch must go hand in hand to search for such parameters.

The potential efficeacy of induction chemotherapy has been advocated since the late 1970s, and clinical trials reproted especially in locally advanced carcinoma of the head and neck[15~19]. Nevertheless, although induction chemotherapy appeared effective on the basis of the response rates, it did not result in prolonging the survival time of a group of patients in randomized studies. This was probably due to the low rates of complete remission, particularly in advanced head and neck cancer, which were only 10~15%, this is similar to our results. Hence, the role of initial chemotherapy in the management of this kind of cancer must be clarified by further study.

SUMMARY AND CONCLUSION

There was a significant correlation between the

response to induction chemotherapy and subsequent radiotherapy except in an early primary tumor (T1, T2) in squamous cell carcinomas of the head and neck. In an early primary tumor (T1, T2) radiotherapy was efficacious despite a failure with induction chemotherapy. The response to induction chemotherapy can be used as a predictive method for the response to subsequent radiotherapy only in locally advanced disease (T3, T4). However, chemotherapy should not be administered solely as an aim for the prediction of response to subsequent radiotherapy. In a locally advanced lesion (Stage III, IV) unresponsive to induction chemotherapy, more effetive treatment strategies (e.g. high LET radiation, hyperthermia, radiosensitizer, modification of fractionation) other than conventional radiotherapy must be sought.

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= 국문초록 =

두경부의 악성종양(편평상피암) 환자에서 유도화학요법에 의한 종양의 관해와 방사선치료에 의한 관해의 상호 관계

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박영환, 심윤상, 오경균, 이용식

유도화학요법과 방사선치료후 종양 관해의 상호 관련성을 파악하고자 1986년부터 1989년까지 원자력병원에서 소정의 충분한 유도화학요법과 근치적 방사선치료를 받은 국소적으로 진행된 두경부 악성종양 환자 60예에 대한 후향적 분석을 시도하였다.

유도화학요법은 CDDP를 기본으로한 복합요법을 2 내지 3회 시행한바, 20예에서 Bleomycin+CDDP(BP), 37예에서 5-FU+CDDP(FP), 그리고 3예에서 BP/FP의 교대요법을 시행하였으며, 방사선은 병소에 따라서 65 Gy 내지 75 Gy 또는 그이상을 조사하였다. 유도화학요법에 의한 종양의 관해율은 원발병소에서는 80%(48/60), 경부임파절에서는 79%(31/39)였으며, 약제, T-병기, 그리고 N-병기에 의한 통계적 유의성은 관찰되지 않았다. 방사선조사 6개월후 원발부위에서는 67%(40/60)의 완전관해를, 경부임파절에서는 77%(30/39)의 완전관해를 보인바, 이를 유도화학요법에 의한 관해 유무에 따른 차이를 분석한 결과 원발부위에서는 유도화학요법에 의한 관해(완전관해 또는 부분관해)를 얻었던 48예중 39예에서 완전관해를 얻었으나(81%), 관해를 얻지못한 12예에서는 1예에서만이 방사선 치료에 의해 완전관해를 얻을 수 있었으며(8%)($p<0.0005$), 경부임파절에서는 유도화학요법에 의해 관해를 얻었던 32예중 28예에서 완전관해를 얻은 반면(90%), 관해를 얻지 못한 8예에서는 2예에서만이 방사선 치료에 의해 완전관해를 얻을 수 있었던바(25%)($p<0.001$), 모두 통계적으로 유의한 차이를 보였다. 한편 이를 원발부위, T-병기 그리고 N-병기에 따라 분석해본 결과, 특히 T-병기중 T3, 4에서는 유의한 차이가 관찰되었으나($p<0.0005$), T1, 2에서는 유의한 차이가 관찰되지 않았다($0.3<p$). 따라서 유도화학요법과 방사선치료에 의한 종양의 관해 정도는 대체적으로 상호연관성이 관찰되고 있으나, 초기 병변에서는 이러한 현상이 관찰되지 않는바 유도화학요법에 의해 관해가 없더라도 방사선 치료에 의해 완전관해를 얻을 수 있을 것이다.