An Analysis of Induction and Adjuvant Chemotherapy in the Multidisciplinary Treatment of Squamous-Cell Carcinoma of the Head and Neck

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This study examines the role of combination chemotherapy with surgery and/or radiotherapy in the initial treatment of patients with advanced stage III and IV squamous-cell carcinoma of the head and neck (SCCHN). Two courses of initial (induction) cisplatin, bleomycin, and methotrexate with oral calcium leucovorin (PBM) were used with the principal intent of increasing the effectiveness of subsequent surgery and/or radiotherapy. Following induction chemotherapy and local treatment, disease-free patients who had responded to initial chemotherapy were entered into a randomized trial of adjuvant PBM. The response rates to induction PBM chemotherapy were a complete response (CR) rate of 26% and a partial response (PR) rate of 52%, for an overall response rate of 78%. A response to induction PBM was highly correlated with failure-free survival ($P < .0001$). A Cox multistep regression analysis of potential prognostic factors was performed. After adjusting for the significant prognostic factors of performance status, initial tumor size, and primary tumor site, a response to induction chemotherapy remained independently associated with improved survival ($P = .0002$). The randomized trial of adjuvant chemotherapy demonstrated that such treatment significantly improved failure-free survival by decreasing local-regional failures. The benefit of adjuvant chemotherapy was particularly evident in patients who had a PR to induction chemotherapy ($P = .01$). The toxicity of this multidisciplinary approach was predictable and acceptable. Surgery and radiotherapy were not compromised by induction or adjuvant chemotherapy. Definitive evidence that chemotherapy can favorably influence survival awaits confirmation of these results by a randomized trial using a control arm of patients treated with conventional surgery and/or radiotherapy alone.
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THE INCIDENCE OF squamous-cell carcinoma of the head and neck (SCCHN) is increasing, with an estimated 40,400 new cases and 13,000 deaths in the United States in 1986.[1,2] Most deaths occur in patients with advanced (stage III and IV) SCCHN, which carries a > 70% 2-year mortality with standard treatment.[3,4] The control of local-regional disease remains the major therapeutic challenge, since morbidity and mortality relate primarily to local invasion and regional lymph node metastases. Distant metastases, while they occur, are a less common cause of first relapse or death.[5]

Major advances have been achieved in the chemotherapy of SCCHN. Several agents are capable of producing tumor regression in 20% to 40% of patients with advanced, previously treated SCCHN.[6] Recent studies using combination chemotherapy in previously untreated patients with advanced SCCHN have reported major objective responses in 70% to 90% of patients, with complete remissions in 20% to 50%.[7–18] In a pilot study of 15 such patients treated at the Dana-Farber Cancer Institute (Boston), a combination of cisplatin, bleomycin, and mid-cycle methotrexate with leucovorin rescue produced a 100% objective response rate.[19] This highly active combination was chosen as the induction and adjuvant chemotherapy for use in this study.

In this study, the use of chemotherapy integrated with surgery and/or radiotherapy for patients with advanced SCCHN was undertaken with three major objectives. The first was to de-

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termine the frequency and magnitude of tumor regression to initial (induction) chemotherapy. The second objective was to determine whether a response to induction chemotherapy altered the curative potential of subsequent surgery and/or radiotherapy. Given that persistent microscopic tumor is a major risk factor for recurrence in patients treated with induction chemotherapy, surgery, and/or radiotherapy,[20,21] the third objective was to determine whether additional (adjuvant) chemotherapy following local treatment was capable of controlling either local-regional disease or distant micrometastatic tumor (see Fig 1 for the experimental design of the study).

METHODS

From October 1, 1979 to April 1, 1983, 144 consecutive, previously untreated patients with stage III and IV SCCHN were referred to the Dana-Farber Cancer Institute and evaluated for this study (Fig 1). Evaluations were performed by a multidisciplinary team in the Head and Neck Cancer Clinic consisting of a head and neck surgeon, a radiotherapist, a medical oncologist, and a dentist. Patients were staged in accordance with criteria established by the American Joint Committee for Cancer Staging.[22] Before study entry, all patients underwent chest x-ray, esophageal contrast, and liver chemistry studies to exclude distant metastatic disease and/or second primary carcinomas. In addition, pulmonary function tests including carbon monoxide diffusion capacity and a 24-hour urinary creatinine clearance were performed on all patients before study entry and each course of cisplatin and bleomycin therapy.

Of the 144 patients, 21 (15%) were excluded from this study for the following reasons: presence of distant metastases (five patients); significant co-morbid disease (four), creatinine clearance of < 50 mL/min (six), and severe compromise in pulmonary reserve with a DLco of < 40% (six). Advanced stage III SCCHN was considered to include all patients with T1-3N1 disease, or T3N0 lesions that were infiltrative in nature or located in the nasopharynx, posterior oropharynx, hypopharynx, base of tongue, or larynx. Of 28 patients presenting with stage III SCCHN, nine did not fulfill the criteria for advanced disease and were excluded from this study. Of the remaining 114 patients, 83% had stage IV disease. Primary tumor extent was predominantly T3 (33%) and T4 (51%), and the extent of regional lymphadenopathy was predominantly N2 or N3 (59%). Written informed consent was obtained. During treatment, patients were seen at least monthly at the multidisciplinary clinic. Follow-up examinations were performed every 1 to 2 months during the first 2 years, and every 3 months thereafter.

Induction Chemotherapy

Cisplatin, 20 mg/m^2/d, was administered as a two-hour continuous infusion on days 1 through 5 with appropriate hydration and antiemetics. Bleomycin, 10 U/m^2/d, was administered as a continuous infusion from days 3 through 7. All patients were hospitalized for cisplatin and bleomycin therapy. On days 15 and 22, methotrexate, 200 mg/m^2, was administered intravenously (IV) and followed 24 hours later by calcium leucovorin rescue, 20 mg orally every six hours for three days. Methotrexate levels were not routinely drawn. A second induction cycle of cisplatin, bleomycin, and methotrexate/leucovorin (PBM) began on day 29.

All patients received two courses of induction PBM chemotherapy and were evaluated for response immediately before local treatment (Fig 1). Tumor responses were defined as complete response (CR), the disappearance of all clinically or radiologically evident tumor; partial response (PR), a > 50% reduction in the product of two perpendicular diameters of all measurable tumor; and no response, anything less than the above. If there was disparity between the response at different sites, the least response was taken as the measure of tumor regression. The durability of tumor regression to chemotherapy could not be considered in the quantification of response, as all patients proceeded directly to local treatment after two cycles of therapy and restaging.

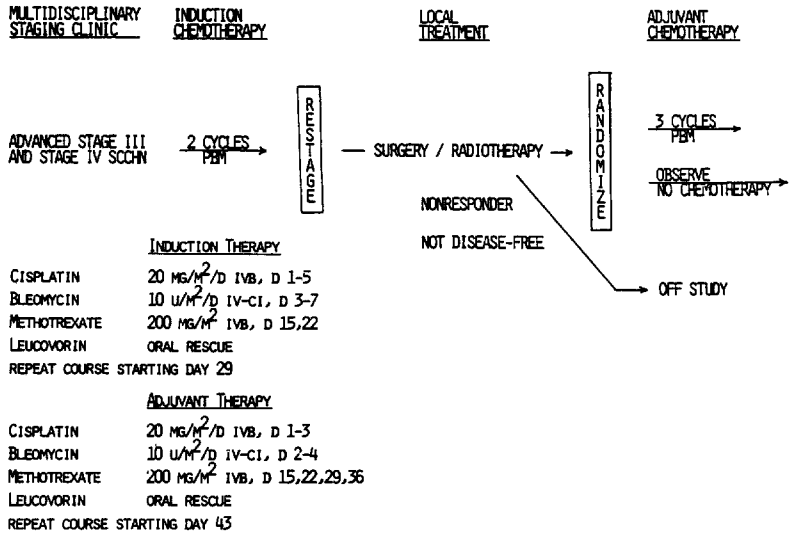


Fig 1. Experimental design of treatment program.

Local Treatment

Local treatment consisted of surgery and/or radiotherapy The anatomic heterogeneity of advanced head and neck cancer makes a precise prospective definition of local treatment difficult. To standardize staging procedures, the same surgeon, radiotherapist, and medical oncologist saw all patients, both initially and following induction chemotherapy Our approach was to deliver maximal local treatment with curative intent based on the initial extent of tumor as determined before induction chemotherapy There was no attenuation of local treatment as a result of tumor regression by induction chemotherapy. This approach was necessary in order to (1) maximize local-regional control, and (2) avoid confounding variables in interpreting local-regional control and survival. The potential advantage of initial chemotherapy might be lost if subsequent local treatment were attenuated.

Surgical resection was undertaken in 58 of 114 patients (51%) and carried out within 3 weeks of the last dose of chemotherapy. Radiotherapy was planned for all patients, and postoperative radiotherapy was preferred. Postoperative radiotherapy consisted of a minimum of 6,000 rad to the regions of the primary tumor bed and involved neck disease. A minimum of 4,500 rad were delivered bilaterally to clinically uninvolved necks.

For 56 patients (49%), radiotherapy alone was administered as the sole form of local treatment. This group included patients who were inoperable or unresectable due to involvement of the nasopharynx, whole tongue, whole floor-of-mouth, or base of skull. In addition, seven of 56 patients (13%) refused a recommended surgical resection and were treated with radiotherapy alone. Radiotherapy was initiated within 4 weeks of the last course of induction chemotherapy Wide treatment fields were planned. A minimum of 6,800 rad in 180 to 200 rad fractions were delivered to the primary tumor bed and involved neck disease. Radiotherapy was usually completed within 8 weeks

Adjuvant Chemotherapy

Following induction chemotherapy, surgery, and/or radiotherapy, patients were considered for adjuvant chemotherapy (Fig 1) Criteria for selection included a CR or PR to induction chemotherapy, evidence that the patient was disease-free following local treatment, acceptable tolerance of induction chemotherapy and local treatment, and the patient's acceptance of randomization. Of the 114 patients in this study, 82 responders to induction chemotherapy were clinically disease free following local treatment, 73 of whom were eligible for randomization. Forty-six patients consented and were randomized to receive adjuvant chemotherapy or no chemotherapy (Table 1). Adjuvant chemotherapy was begun within 4 weeks of the last radiation treatment and consisted of three 42-day cycles of reduced-dose PBM chemotherapy (Fig 1).

Statistical Methods

The method of Kaplan and Meier[23] was used to estimate failure-free survival and overall survival curves. Failure, in the failure-free survival curves, was defined as (1) tumor progression or death, whichever came first, for patients not rendered free of disease, (2) relapse for patients rendered free of disease; and (3) death that was treatment related. Failure-free and overall survival were measured from study onset; the effect of response to induction chemotherapy on failure-free survival was measured from the onset of local treatment, and the impact of adjuvant chemotherapy on failure-free survival was measured from the time of randomization.[24]

The relationship of various patient characteristics on response to induction PBM and failure-free survival was analyzed (Table 1) by log rank test.[25] The proportional hazards model, as proposed by Cox[26] was used to analyze these relationships while adjusting simultaneously for other patient characteristics. A Cox model was used to test whether response to induction chemotherapy was predictive for an improved failure-free survival in the presence of other covariates First, a step-up algorithm[27] was used to select important covariates, then response was added to see if response and the degree of response were predictive. Only 110 of 114 patients (95%) who were alive at the end of induction chemotherapy (60 days) were considered in this Cox analysis (Landmark method).[24]

The word "significant" is used when a P value was ≤ 0.05. All tests were based on two-sided alternatives.

RESULTS

Of the 114 patients, a complete remission with induction chemotherapy alone was achieved in 26% and a partial remission in 52% of patients for a total response rate of 78% (Table 1).

The distribution of patients by such potential prognostic variables as age, sex, performance status, primary tumor site, stage, and tumor size at study entry is presented in Table 1. Neither age (including age over 70 years), sex, nor stage predicted for response or failure-free survival. Factors predicting a significantly improved failure-free survival included a good performance status (ECOG 0 to 2; $P = .02$), a small initial tumor size (< 7 cm in greatest tumor diameter; $P = .03$), and a nasopharyngeal primary tumor site ($P = .02$).

The effect of response to induction chemotherapy on failure-free survival is presented in Fig 2. Because of the close correspondence between failure-free and overall survival (Fig 3), failure-free survival was reported in Figs 2, 4, and 5. The presence and magnitude of tumor regression with induction chemotherapy had a significant influence on failure-free survival (Fig 2). Patients exhibiting a CR to induction chemotherapy before local treatment had a 3-year failure-free survival of 83%, while those achieving a PR had a failure-free survival of 44%. Patients not responding to induction chemotherapy had a median failure-free survival of 6 months, and all but two patients had relapsed by 18 months.

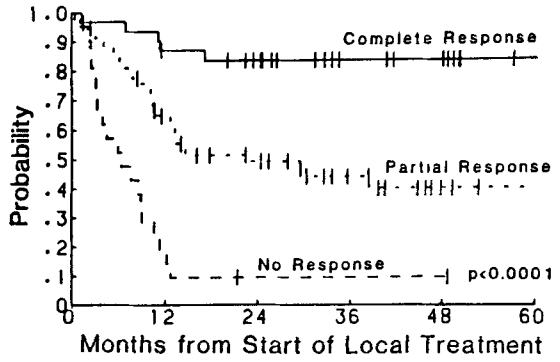
It is a common observation that a response to chemotherapy is more likely to occur in patients with favorable prognostic characteristics such as

performance status, initial tumor burden, and age.[24] Thus, a response to chemotherapy may not be independently associated with an improved survival. To address this problem, a Cox multistep regression analysis was performed to determine the power and independence of a response to chemotherapy on failure-free survival. All potential prognostic factors were analyzed and four were found to correlate with a favorable failure-free survival when analyzed individually: a better performance status ($P = .02$), a nasopharyngeal primary site ($P = .02$), a small initial tumor size ($P = .03$), and, in particular, a CR to induction chemotherapy ($P < .0001$). When the multistep regression analysis was performed, initial tumor size did not independently predict for failure-free survival, whereas performance status ($P = .01$) and a nasopharyngeal primary site ($P = .03$) remained significant. When adjustments were made for performance status, initial tumor size, and primary tumor site, it was found that a response to induction chemotherapy remained the most powerful ($P = .0002$) and independent predictor for failure-free survival.

Table 1. Analysis of All Study Patients by Prognostic Category, Response to Induction Chemotherapy, and Failure-Free Survival

Characteristics	Response Data: No. of Patients (%)	CR (%)	CR and PR (%)	2-yr Failure-Free Survival* (%)	Adjuvant Study Entry: Eligible for Randomization	Randomized: Treated	Randomized: Observed
Total	114	26	78	50	73	26	20
Age							
< 49	22 (19)	23	82	63	17	8	5
50–59	32 (28)	19	63	42	15	8	3
60–69	38 (33)	32	90	57	29	8	12
70–79	22 (19)	32	77	39	12	2	0
Sex							
Male	83 (73)	24	76	54	53	17	13
Female	31 (27)	32	84	42	20	9	7
Performance status (ECOG)							
Asymptomatic	48 (42)	15	79	51	32	9	11
Minor symptoms (ECOG 3, 4)	38 (33)	37	76	58	26	10	5
In bed < 50% (ECOG 2)	20 (18)	36	80	43	13	7	2
In bed > 50% (ECOG 1)	8 (7)	25	75	25	2	0	2
Primary site							
Tongue†	20 (18)	50	85	54	15	5	4
Oral cavity‡	11 (10)	9	91	45	8	3	3
Tonsil	15 (13)	—	80	41	8	4	1
Oropharynx	7 (6)	43	71	57	4	1	1
Hypopharynx	28 (25)	29	79	43	20	6	7
Larynx§	12 (11)	17	58	50	6	2	1
Nasopharynx	12 (11)	33	92	83	10	4	3
Other sites ‖	9 (8)	22	56	38	2	1	0
Stage							
III	19 (17)	53	95	53	15	4	6
IV	95 (83)	21	75	50	58	22	14
Size of tumor¶							
3–4 cm	22 (19)	32	87	54	16	5	4
5–6 cm	63 (55)	27	86	65	45	15	16
≥ 7 cm	28 (25)	21	57	37	12	6	0

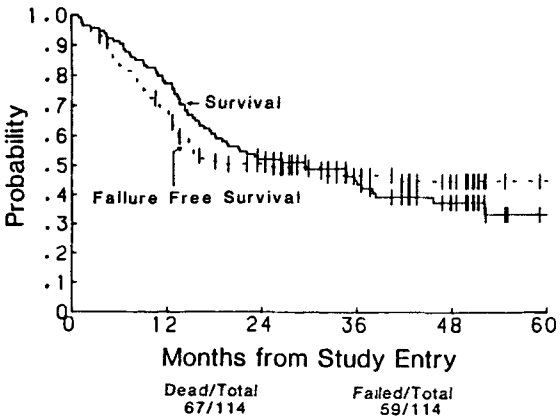
*Kaplan-Meier estimate of failure-free survival (Kaplan-Meier estimate).
†Includes ten of 20 base of tongue.
‡Includes cheek and floor-of-mouth.
§Includes supraglottic larynx.
‖Includes ear, sinus, nose, and unknown primary site.
¶Greatest diameter of largest single tumor mass before any treatment.



Response	Failed/Total
Complete	5/30
Partial	31/59
None	19/21

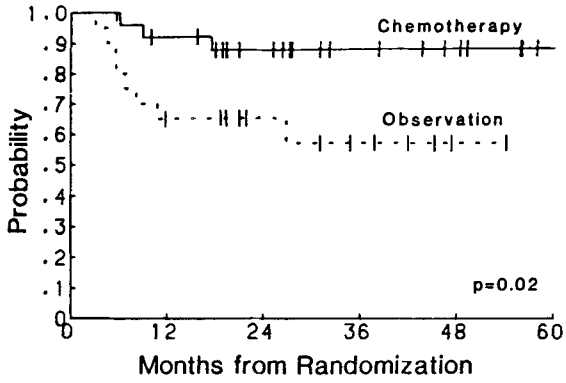
Fig 2. The effect of response to induction PBM on failure-free survival.

As noted, 89 of 114 patients (78%) had an objective response to induction chemotherapy. Of these 89 patients, 82 (92%) were clinically and radiographically disease free after completion of local treatment. Nine patients (11%) were not eligible for the trial of adjuvant chemotherapy for medical reasons. These reasons included major toxicity with induction PBM or significant or prolonged morbidity related to local treatment. Thus, 73 patients were eligible for randomization to adjuvant chemotherapy, of whom 46 (63%) accepted. Twenty patients were randomized to receive no chemotherapy (control group) and 26 to receive adjuvant chemotherapy. Treatment and observation groups were well balanced with respect to potential prognostic factors (Table 1).



Dead/Total	Failed/Total
67/114	59/114

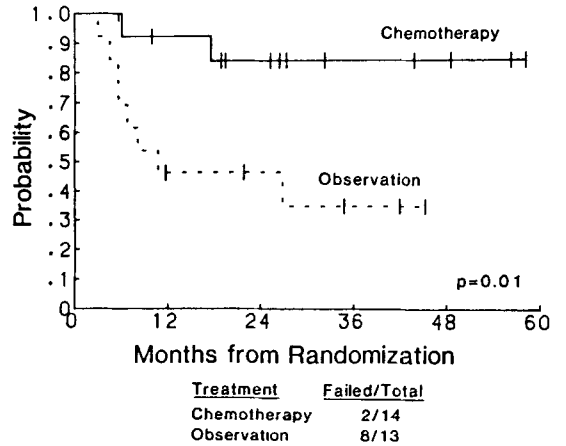
Fig 3. Failure-free and overall survival by actuarial estimate from study entry for the 114 patients treated in this study.



Treatment	Failed/Total
Chemotherapy	3/26
Observation	8/20

Fig 4. The effect of adjuvant chemotherapy on failure-free survival for the 46 patients in the randomized trial of adjuvant chemotherapy.

The 46 patients randomly allocated to adjuvant chemotherapy or observation following local treatment are presented in terms of failure-free survival in Fig 4. For patients receiving adjuvant chemotherapy, the estimate of failure-free survival 3 years following the completion of surgery and/or radiotherapy was 88%, as compared with 57% for control patients ($P = .03$). The failure-free survival for the 27 patients who were eligible for the adjuvant chemotherapy trial but who refused randomization was not significantly different from that for randomized control patients. When the 46 patients were subdivided into groups treated with surgery and radiotherapy (29 patients) or radiotherapy alone (17 patients)



Treatment	Failed/Total
Chemotherapy	2/14
Observation	8/13

Fig 5. The effect of adjuvant chemotherapy on failure-free survival for patients achieving a PR to induction chemotherapy.

and analyzed separately, trends toward improved survival for patients receiving adjuvant chemotherapy were noted, but significantly improved survival with adjuvant treatment was apparent only when both groups were combined. Because of the low failure rate of all patients achieving a CR to induction PBM (Fig 2) and the small number of patients in the adjuvant study, an advantage to adjuvant PBM could not be demonstrated in that group. When patients achieving a PR to induction PBM were analyzed separately, the estimate of failure-free survival 3 years following completion of local treatment was 84% for those patients receiving adjuvant chemotherapy, as compared with 35% for control patients (P = .02; Fig 5). These data suggest that patients with a PR to induction PBM are at a greater risk for persistent tumor following surgery and/or radiotherapy than patients with a CR, and that adjuvant chemotherapy can reduce this risk. Of the 11 failures that developed in the 46 patients entered in the randomized trial of adjuvant chemotherapy, all were local-regional (ten local-regional, one local-regional plus distant).

Failure-free and overall survival for the 114 study patients are presented in Fig 3 with a minimum follow-up of 25 months from study entry. The failure-free and overall survival curves are similar up to 24 months. The risk of relapse (failure) in patients with treated SCCHN is known to be greatest during the first 2 years after initiation of treatment, following which relapse is infrequent.[28] This is evident in the failure-free survival curve, which is essentially flat at 45% after 24 months. However, overall survival continued to decline through 6 years to 33% reflecting mortality due to cardiovascular disease and a variety of second primary carcinomas. At the time of this analysis, there were 34 recurrences in the 91 of 114 patients (80%) considered disease free at the end of surgery and/or radiotherapy. Of these recurrences, 24 were local-regional, five were local-regional with synchronous or metachronous distant metastasis, and six were distant only.

The toxicity to induction PBM chemotherapy is presented in Table 2. Nausea and vomiting were generally well controlled by antiemetics, particularly perphenazine and pentobarbitol. Reversible nephrotoxicity occurred in 20% of patients and was attributed to cisplatin in 15% and methotrexate in 5%. In 23% of patients, dose

Table 2. Frequency of Toxicity to Induction PBM

Toxicity	Total (%)	Mild (%)	Moderate (%)	Severe (%)	Lethal (%)
Nausea/vomiting	46	35	10	1	—
Thrombocytopenia	45	18	13	14	—
Leukopenia	30	19	6	5	—
Nephrotoxicity	20	7	6	7	—
Mucositis	14	5	4	5	—
Fever	9	5	2	2	—
Rash	7	3	1	3	—
Respiratory*	5	3	1	—	1
Diarrhea	2	1	1	—	—

NOTE. Toxicity code criteria: nausea/vomiting: mild = nausea only, moderate = vomiting controlled during chemotherapy, and severe = vomiting uncontrolled after chemotherapy finished; thrombocytopenia: 0 = > 150,000, mild = 100,001 to 150,000, moderate = 50,000 to 100,000, and severe = < 50,000; leukopenia: 0 = > 2000, mild = 1,001 to 2,000, moderate = 501 to 1,000, and severe = 0 to 500; nephrotoxicity (peak creatinine × baseline): 0 = < 1.25, mild = 1.25 to 1.50, moderate = 1.5 to 2.0, and severe = > 2.0. Respiratory: 1 = asymptomatic CXR infiltrates; 2 = exertional dyspnea; 3 = dyspnea at rest.

*Drug related.

modifications were made during induction chemotherapy. In five cases only one course of PBM was administered. Two patients received no methotrexate, and 12 patients had attenuated doses of methotrexate due to nephrotoxicity. An additional six patients had dose reductions due to myelosuppression or a debilitated state. Four patients died during induction chemotherapy: one of pulmonary embolus, one of myocardial infarction, one of aspiration pneumonia, and one of bleomycin and/or methotrexate toxicity. Only the latter was clearly treatment related. Less frequent toxic manifestations (< 9% of patients) consisted of rash, diarrhea, and fever, all of which were reversible and did not compromise drug delivery.

Toxicity from the adjuvant program was qualitatively similar to that of induction chemotherapy. Quantitatively, myelosuppression, central nausea and vomiting, and nephrotoxicity were less frequent and less severe. Oral mucositis was more common (30% of treated patients), possibly due to the poor tolerance of irradiated oral mucosa to subsequent methotrexate and/or bleomycin. Mucositis and excessive patient fatigue were the principle reasons for terminating adjuvant PBM. Of the 26 patients randomized to re-

ceive adjuvant chemotherapy, three refused treatment after randomization, three received one course of therapy, ten received two courses, and ten patients received all three planned courses of treatment.

Complications of local treatment with surgery and/or radiotherapy included seven patients with a weight loss of more than ten pounds, three postoperative wound infections, one case of wound breakdown, and two cases of osteoradionecrosis in patients with composite resection and postoperative radiotherapy. One patient died of pulmonary embolism in the postoperative period and another of aspiration pneumonia during radiotherapy. Local toxicity associated with surgery was not more severe than that expected in the absence of prior chemotherapy. The use of induction chemotherapy appeared to accelerate the appearance of radiation mucositis, but did not substantially alter treatment scheduling.

DISCUSSION

The intent of this study was to analyze the role of sequential combination chemotherapy in the multidisciplinary treatment of patients with advanced SCCHN. Local-regional control of tumor and survival for patients with advanced SCCHN treated with surgery and/or radiotherapy alone has been poor.[3,4] The purpose of induction chemotherapy was to promote initial tumor regression (stage reduction) and enhance local-regional control of tumor, provide early treatment for occult micrometastatic disease, and identify a patient population that might benefit from similar chemotherapy administered as additional adjuvant treatment following surgery and/or radiotherapy. The purpose of adjuvant chemotherapy was to eradicate occult local-regional disease or distant metastases that remained after induction chemotherapy and local treatment.

The chemotherapy combination used in this study was formulated with the expectation of improved response rates over those seen with single agents. The regimen of cisplatin, bleomycin, and methotrexate contains three of the most active single agents in the treatment of patients with recurrent or metastatic disease. Each agent is individually capable of producing significant, although short lived, tumor regession in 20% to 30% of such patients.[29] The combination of cisplatin and bleomycin has been previously reported by several investigators to have substantial activity against SCCHN.[7,8,12] The use of midcycle intermediate dose methotrexate and leucovorin rescue with cisplatin and bleomycin provides additional non–cross-resistant therapy that might prevent early relapse without aggravating preexisting mucositis or myelosuppression. The activity of this three-drug combination (PBM) was initially evaluated in a phase II study at the Dana-Farber Cancer Institute. In 29 patients with advanced SCCHN (48% previously treated), PBM resulted in objective tumor regression in 100% of patients, with complete clinical regression of tumor in 27%.[19]

For the present study, the decision to use two cycles of induction chemotherapy represented a compromise between those physicians interested in maximizing response rates to induction chemotherapy, and those physicians concerned that an excessive delay in definitive local treatment might jeopardize survival. The decision to limit adjuvant treatment to three courses of a dose-attenuated regimen of PBM chemotherapy was based on the expected toxicity of the regimen and patient compliance after a minimum of 4 to 5 months of induction chemotherapy and local treatment.

The first objective of this study was to determine the frequency and magnitude of objective tumor regression with induction PBM. Such regression occurred in 78% of patients, with complete clinical resolution of disease in 26%. Of patients achieving a CR who subsequently underwent a surgical resection, five of 15 patients (33%) had no tumor identified on histopathologic analysis of the operative specimen. All patients with a pathologic CR remain disease free at this writing. These results indicate that a common epithelial tumor, SCCHN, is highly sensitive to chemotherapy, with response rates exceeding those for patients with metastatic breast cancer and approaching those for patients with advanced lymphoma. Similar observations in untreated patients with advanced SCCHN have been reported.[7–18]

The second major objective in this study was to determine whether chemotherapy used as induction treatment could improve the effectiveness of surgery and/or radiotherapy in terms of local-regional control of tumor and survival. The 2-year failure-free and overall survival rates in

this study were 50%. Other reports concerning the treatment of advanced stage III and IV disease with conventional surgery and/or radiotherapy indicate a 2-year relapse-free survival of only 10% to 30%.[3,4] However, considering the heterogeneity of this disease and problems related to patient selection and differing local treatment programs, the comparison of our survival rates to those of other studies has limited meaning.

In this study, a highly significant positive correlation was found between a response to induction chemotherapy and failure-free survival. For patients achieving a CR to induction PBM, the 3-year estimate of failure-free survival was 83%, while that for patients with a PR was 44%, and that for patients without a response was 10% (Fig 2). When all potential prognostic factors for response and survival were isolated and analyzed, a good performance status, and a low initial tumor burden, a nasopharyngeal primary site, and a response to induction chemotherapy were associated with an improved failure-free survival. A Cox regression analysis, which adjusts for the various prognostic factors, was performed to determine the power and independence of these individual factors. With this analysis, initial tumor burden was no longer a significant prognostic factor, but a good performance status and a nasopharyngeal primary site were independently predictive for an improved failure-free survival. Using the same technique, a response to induction chemotherapy was found to be the most significant and independent predictor for failure-free survival.

The finding that a response to induction chemotherapy is associated with an improved survival has been previously reported in several uncontrolled trials of induction chemotherapy for patients with advanced SCCHN.[11,18,30–32] However, it should be recalled that such an association does not prove a causal relationship. For example, a response to induction chemotherapy may select patients who would have fared equally well with conventional local treatment alone. There is evidence that tumors that respond to induction chemotherapy are sensitive to subsequent radiotherapy.[33] It has not yet been determined whether this radiosensitivity is intrinsic to the untreated tumor or secondary to initial chemotherapy and tumor regression. Ultimately, rigorous proof of an impact of induction chemotherapy on survival requires analysis by a randomized trial that contains a control arm of patients treated by surgery and/or radiotherapy alone.

Previous reports of induction chemotherapy for advanced SCCHN have been negative or questionably positive for improved survival. Studies reporting improved survival with induction chemotherapy have used high doses of combination chemotherapy for at least 2 months before conventional surgery and/or radiotherapy, but these studies were not controlled trials.[9,11,18] To date, nine randomized controlled trials of induction chemotherapy for advanced SCCHN have been published, and none has reported an improved survival with induction chemotherapy before local treatment.[34–42] However, the impact of induction chemotherapy on survival in most of these trials may have been lessened by the use of single-agent chemotherapy[34–37] or combination chemotherapy of limited duration.[38,39] Only three trials have administered more than one cycle of induction combination chemotherapy. Holoye et al[41] administered either one or two cycles of an induction regimen that did not contain cisplatin, reported a CR rate of only 10%, and failed to note the percentage of patients receiving only one course of treatment. Hass et al[42] used up to three cycles of cisplatin with continuous-infusion 5-fluorouracil, but reported a CR rate of only 17%. This low rate of CR was unexplained and remains in sharp contrast to the CR rate of 54% achieved with an identical induction regimen in an uncontrolled trial at another institution.[16] Schuller et al[40] reported 73 patients with resectable advanced SCCHN treated with a 9-week, three-course regimen of combination chemotherapy before local treatment. In this trial, total and CR rates of 65% and 20%, respectively, were achieved, but an improved survival was not associated with initial chemotherapy. This study has been criticized for the use of less than maximal doses of cisplatin in the induction regimen and the administration of only 5,000 cGy postoperative radiotherapy.

Apart from problems with experimental design, limited follow-up evaluation, or inadequate patient accrual, the inability to document an improved survival with induction chemotherapy may relate to attenuation of local treatment deliv-

ered to patients receiving chemotherapy. In general, the randomized studies have not adequately reported whether surgery and/or radiotherapy was limited in selected patients who had a major response to induction chemotherapy. Such reductions were present in the study by Stell et al,[38] and may have compromised survival in patients treated with induction chemotherapy.

That chemotherapy can favorably influence the natural history of advanced SCCHN is most strongly suggested by the results of our trial of additional adjuvant chemotherapy. In this study, a dose-attenuated regimen of PBM was offered in a randomized control trial to 46 patients who had initially responded to induction PBM and were clinically disease free after local treatment. For the 26 patients who received both induction and adjuvant chemotherapy, survival and local-regional control were improved compared with a control group of 20 patients treated with induction chemotherapy and local treatment alone. Further analysis indicated that a significant benefit from adjuvant chemotherapy was restricted to the subgroup of patients with a PR to induction chemotherapy (Fig 5). The failure-free survival of patients who achieved a CR to induction PBM was excellent (over 80%) and not significantly affected by additional chemotherapy. For patients with a PR to induction PBM, the 3-year failure-free survival for patients receiving additional adjuvant chemotherapy was 84%, as compared with 35% for the control group of patients. It would be expected that patients who achieved a PR to induction chemotherapy are at a greater risk for local-regional failure following local treatment than patients achieving a CR. It appears that adjuvant chemotherapy can reduce this risk for patients with a PR to induction chemotherapy.

Although only 46 patients entered the trial of additional adjuvant chemotherapy, these data represent the first direct evidence by randomized trial that the use of combination chemotherapy can favorably alter the natural history of advanced SCCHN. While others have evaluated both induction and adjuvant chemotherapy,[30,37,38,43] only two studies have addressed the use of adjuvant chemotherapy by randomized trial. Neither Tejada and Chandler[44] nor the Head and Neck Contracts Program[39] reported a survival benefit with adjuvant chemotherapy. However, both of the latter trials reported significant toxicity with adjuvant chemotherapy resulting in periodic interruptions of treatment and poor drug compliance. The apparent success of the Dana-Farber trial of adjuvant chemotherapy may be related to the specific dose-attenuated regimen of adjuvant chemotherapy used, to the acceptable performance status of patients consenting to participate in the randomized trial, or to the fact that patient eligibility was restricted to those who had responded to initial induction chemotherapy.

Disseminated micrometastases are not the predominant site of relapse in patients with advanced SCCHN occurring clinically in only 25% of patients.[4,5,27] In our series, 11 of 91 patients (12%) who were disease free after surgery and/or radiotherapy developed distant metastases without local-regional recurrence. This number was too small to determine the impact of chemotherapy on the control of micrometastatic disease. That adjuvant chemotherapy was superior to observation alone in the control of local-regional disease would suggest that chemotherapy may be capable of irradicating disseminated micrometastatic disease in patients with SCCHN.

While the benefit of chemotherapy with surgery and/or radiotherapy for patients with SCCHN remains an unsettled question, so too remains the extent of local treatment necessary after induction chemotherapy. Preliminary evidence suggests that selected patients with advanced SCCHN may be effectively treated with radiotherapy alone following a histologically confirmed CR to induction chemotherapy.[32] However, local-regional failure remains a significant problem despite maximal surgery and radiotherapy for patients achieving only a PR to induction chemotherapy. Our randomized study of adjuvant chemotherapy suggests that the risk of local-regional failure can be reduced and failure-free survival prolonged through the use of additional chemotherapy for those patients with a PR after 2 months of induction chemotherapy.

The management of patients who fail to respond to induction chemotherapy also remains in question. All studies of induction chemotherapy that stratify local-regional control of tumor or failure-free survival by response to chemotherapy report the dismal outcome of this subgroup of patients.[11,17,18,33] Therapeutically, highly morbid and debilitating surgical resections may not be

appropriate if there is no response to induction chemotherapy. For such patients, combined modality therapy with surgery and radiotherapy may not enhance local-regional control of tumor or survival compared with definitive radiotherapy alone.[17]

In order to determine definitively the role of chemotherapy in the multidisciplinary treatment of patients with advanced SCCHN, new randomized trials comparing conventional surgery and/or radiotherapy with induction combination chemotherapy before local treatment are indicated. Such studies should include at least 2 months of high-dose induction combination chemotherapy and maximal local treatment plus additional chemotherapy for those achieving a PR to induction chemotherapy. Whether the additional chemotherapy for PRs should be in the form of adjuvant chemotherapy, or prolonged courses of induction chemotherapy, is not known. Adjuvant chemotherapy may not benefit patients who achieve a CR to induction chemotherapy. Accepting the proposition that a response, and particularly a CR, to induction chemotherapy will improve survival following surgery and/or radiotherapy, research should be directed toward the development of more effective regimens of combination chemotherapy, which will lead to even higher rates of CR. This approach has been successful in the development of curative treatment for the acute leukemias, the lymphomas, and for testicular carcinoma.[45]

In summary, (1) induction PBM chemotherapy in patients with advanced, previously untreated SCCHN produced objective tumor regression in 78% of patients, with complete clinical regression in 26%; (2) the presence and magnitude of tumor regression with induction chemotherapy was associated with an improved failure-free survival after surgery and/or radiotherapy independent of other prognostic factors; and (3) in a randomized controlled study of patients who responded to induction PBM and were disease-free after local treatment, the use of additional adjuvant PBM chemotherapy significantly and favorably influenced local-regional control of tumor and failure-free survival.

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