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Patterns of Response and Relapse in Chemotherapy of Extensive Squamous Carcinoma of the Lung

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Summary. *In a large study of combination chemotherapy for patients with extensive squamous carcinoma of the lung, 44 of 247 patients (18%) achieved > 50% regression of tumor mass. The likelihood of response was significantly (and independently) higher for females and for fully ambulatory patients. Bone and liver were the most commonly involved metastatic sites, with documented involvement pretreatment in 32 and 16% of patients, respectively. Recurrence in the ipsilateral hemithorax after radiation therapy was the only clinical evidence of disease in 24% of the patients. There were no significant differences in response rate by individual metastatic sites, or for single compared to multiple sites. The median time to response was 4 weeks, with response noted by 8 weeks in 74%.*

Clinically evident relapse has occurred in 39. Among these, the primary site was the only clinical site of failure in 14, of whom 7 never received radiation therapy. The brain was the only site of initial failure in 6, only 1 of whom had preexisting evidence of brain involvement. Failure in a single area of previously evident disease or the brain accounted for 74% of recurrences in the responding group. These observations suggest that sequential, planned radiation therapy to sites of previous clinical involvement, together with 'prophylactic' whole-brain radiation, may be of benefit in the drug-responsive subpopulation of patients with extensive disease.

Introduction

The treatment of extensive squamous carcinoma of the lung has been a frustrating exercise for the chemotherapist, and in general an unrewarding one for the patient. Although objective responses are observed in an appreciable fraction of the patient population, they have yet to be translated into meaningful survival benefit, even for the subpopulation of responders. This relates both to the toxicity of available chemotherapy and to the fact that most responses are only partial, rarely exceeding a few months in duration.

Between December of 1974 and October of 1976, the Southwest Oncology Group undertook a large study of combination chemotherapy (BACON vs. NAC) in patients with extensive lung carcinoma of squamous histology, the results of which have been reported elsewhere (Livingston et al., 1977). What has not been previously reported in this study, nor, to our knowledge, in any study of chemotherapy in this disease, are the specific characteristics of response and relapse, among those achieving measurable objective regression.

Materials and Methods

The records of 247 consecutive patients who were entered into this study were reviewed. Each had a diagnosis of squamous carcinoma of the lung, based on review by the pathologist at the referring institution. There was no centralized review, and characterization of the pathologic material by degree of differentiation was not available. The patients all received combination chemotherapy with one of two regimens, to which they were randomly allocated: nitrogen mustard at 8 mg/m^2 IV every 4 weeks, adriamycin at 40 mg/m^2 IV every 4 weeks, and CCNU at 65 mg/m^2 PO every 8 weeks (NAC); or the same three drugs plus vincristine, 0.75–1.0 mg IV weekly for 6 weeks, followed each time in 6 h by bleomycin, 30 units IV or IM (BACON). No patients received radiation therapy, except as their physicians felt it necessary for the palliation of symptoms. In practice, this amounted to the use of radiation to control brain metastasis, superior vena caval syndrome (when not already so treated), and painful bony metastases. Eligibility for the study required extensive spread, meaning clinical evidence of involvement beyond the hemithorax and adjacent supraclavicular nodes, and/or regional recurrence in the chest after radiation to the primary site. Those patients who achieved more than 50% regression of objectively measurable lesions for at least a month were considered responders, provided they had no evidence of progression or new disease in any site.

A stepwise logistic regression procedure was applied to the prediction of response probability, based on consideration of 25 pretreatment prognostic variables. Details of this procedure are described elsewhere (Heilbrun and Livingston, 1978); the pretreatment variables are shown in Table 1.

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Table 1. Pretreatment sites of involvement and response

Site of measurable disease	Number of times involved (%)	Number of times responding (%)
Ipsilateral hemithorax	189 (77)	30 (16)
Bone	81 (33)	10 (12)
Liver	40 (16)	10 (25)
Brain	32 (13)	1 (3)[a]
Lymph nodes	50 (20)	8 (16)
Other lung	24 (10)	4 (13)
Skin and soft tissue	16 (6)	3 (10)

[a] All patients with brain involved received whole-brain radiation (see text)

Table 2. Response in ipsilateral hemithorax by prior radiation therapy status

Category pretreatment	Number of patients (% of total)	Number of responses (% of category)
Prior radiation	98 (40)	11 (11)
to primary tumor:		
'Chest only'	59 (24)	7 (12)
'Chest + other'	39 (16)	4 (10)
No prior radiation to primary tumor[a]	91 (37)	19 (21)

[a] All had clinical evidence of spread beyond the hemithorax and adjacent node-bearing areas

Results

A total of 44 patients (18%) demonstrated objective response to chemotherapy, for a median duration of 22 weeks. Only 4 patients achieved a complete response. There were no significant differences in response rate or duration between the two treatment arms. The two pretreatment prognostic variables which had a significant association with likelihood of response were female sex ($P = 0.005$) and fully ambulatory performance status ($P = 0.045$). Females had a 32% response rate, compared to 14% for males. Fully ambulatory patients (Karnofsky performance status 8–10) had a 27% response rate, compared to 13% for those who entered with lesser functional status. No significant interaction was found between sex and performance status ($P > 0.5$), in terms of their association with response likelihood.

Time to response ranged from 2 to 20 weeks, with a median of 4. Response was observed by 8 weeks in 32/43 for whom this information was available (74%). Response was documented more quickly (and more frequently) in those sites which could be verified by physical exam or chest X-ray.

The pretreatment sites of involvement which could be measured, and the response frequency per site, are summarized in Table 1. Overall, response was noted in 66 sites (mean, 1.5/responder) among 432 measurable sites (mean, 1.75/patient). Response was attributed only once to chemotherapy for the brain, a site which was universally treated by radiation therapy (this was in a patient who had already received whole-brain radiation, with recurrence). Otherwise, the response frequency by site varied from 12% for bone to 25% for liver. None of these differences are significant. Nor were there any significant differences in response rate related to the number of metastatic sites pretreatment.

The frequency of response in the hemithorax corresponding to the primary site (ipsilateral hemithorax) was then examined, according to whether or not the patient had received radiation therapy to the primary tumor prior to entry on study. Only patients with measurable disease were considered (of 125 with prior radiation to the primary, 98 (78%) entered the study with definable ipsilateral disease). The results of this analysis are shown in Table 2. Among those with prior radiation, those who had no measurable disease outside the hemithorax are called 'chest only'; the remainder, 'chest + other,' had measurable recurrence in the ipsilateral chest as well as other areas. The response rate is higher for patients without prior radiation, 21 vs. 11%. This difference was not statistically significant at the level of $P < 0.05$ (chi squared = 2.61).

The sites and frequency of initial clinical relapse are shown in Table 3. Relapse has occurred in 39/44 responders (89%). Two of the patients continue in complete remission, one of whom is beyond two years (involvement pretreatment was in cervical nodes and ipsilateral hemithorax + bone, respectively). One patient was lost to followup after he refused further treatment; a second committed suicide; and a third died of pneumonia while still responding clinically. Among the 39 relapsing patients, the ipsilateral hemithorax was the sole site of initial failure in 14 (36%), of whom 7 never received radiation to the primary site. The brain was the only clinical site of initial relapse in 6 (15%), only 1 of whom had brain involvement initially. Four patients had clinical relapse confined to the liver: all had pretreatment hepatic involvement. Another 5 patients had relapse initially in a single site of previous clinical involvement (soft tissue mass, 1; supraclavicular nodes, 2; paratracheal mass, 1; bone, 1). Two of these had received radiation to the primary tumor; none had received it specifically to these areas of involvement. A total of 9 patients (23%) had relapse in a site (other than brain) which was not previously involved (bone, 4; marrow, 1; liver, 1; larynx, 1; nodes, 1; soft tissue, 1). Four of these 9 failed simultaneously in sites of previous involvement. The remaining patient relapsed in multiple sites of previous pulmonary involvement, bilaterally.

Table 3. Sites of initial clinical relapse

Number of responders	Number with relapse	Single area of relapse, previously involved:			Brain	Multiple or new sites
		1° site	Liver	Other		
44	39	14	4	5	6	10
Per cent of all relapses:			59		15	26

Discussion

In our study, female sex and fully ambulatory performance status were pretreatment prognostic factors of independent significance in predicting the likelihood of response. Thus, although the overall response rate was only 18%, the same chemotherapy could be expected to produce response rates in the range of 30% in a population which was relatively favorable with respect to either of these parameters. On the other had, this study offers no evidence that the site or multiplicity of metastasis is a factor which affects response likelihood, with the exception of the known low probability that brain metastasis will respond to chemotherapy.

It is impossible to draw definite conclusions about the influence of prior radiation therapy on the chance of achieving a response in the corresponding hemithorax. A clinical impression exists that 'local' response is seen less frequently in such patients, which is supported by the observation that only 11% of measurable 'local' lesions responded to chemotherapy if the primary tumor had been radiated, while 21% of such lesions responded in patients without prior radiation. But this difference is not marked enough, with the numbers involved, to achieve statistical significance.

The most important finding from this analysis is that relapse from response tends to follow an orderly, predictable pattern in the vast majority. Three-fourths of the time, a single site of previous involvement signaled the end of response. Almost two-thirds of the relapses occurred in chest, brain, or liver as a single site. These observations, together with the evidence that whole-brain 'prophylactic' radiation can reduce the incidence of de novo brain metastasis (Moore et al., 1978) in small cell carcinoma and non-small cell disease (Cox et al., 1977), support the intentional, sequential administration of radiation therapy to the brain and sites of previous involvement among patients with extensive squamous carcinoma of the lung who respond to chemotherapy. This might result in an increase in the complete response rate and the duration of remission with real survival benefit in the responsive subpopulation.

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