Central Nervous System Involvement and the Role of Prophylactic Cranial Irradiation in Small Cell Lung Cancer

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Key Words. Small cell lung cancer (SCLC) · Prophylactic cranial irradiation (PCI) · Brain CT-Scan · Central nervous system (CNS) metastases

ABSTRACT

This paper studies the frequency and manifestations of central nervous system (CNS) involvement and assesses the role of prophylactic cranial irradiation in small cell lung cancer (SCLC). All patients with confirmed diagnosis, admitted to our department within the last 15 years, were included. Patients were staged as having limited or extensive disease. Irradiation (40 Gy/20f) was offered to all complete responders immediately after polychemotherapy. There were 200 patients (176 men and 24 women, median age 58), 68 with limited and 132 with extensive disease. Twenty (10%) presented with CNS involvement, 14 (7%) developed it during chemotherapy and 47 (23.5%) during follow-up. In total, 81 (40.5%) developed CNS involvement, and in 57 (28.5%) it was the main manifestation. There was no relation to disease extent or type of response to therapy. The most frequent site of metastases was brain (33%), followed by leptomeninges (6%), spinal cord (1.5%), and pituitary (1.5%).

Of 79 complete responders, 51 (65%) received prophylactic cranial irradiation (PCI) and 28 (35%) did not. Frequency of CNS involvement was not significantly different (49% and 39%, respectively). Actuarial probabilities of developing CNS involvement were also not different. Nevertheless, 91% of complete responders without PCI relapsed only to CNS involvement, versus 48% with prophylactic irradiation. Cranio prophylaxis administration was followed by an improvement in overall survival, which was highly significant in limited disease. The actuarial survival of complete responders at two and four years was 46% and 26% with cranio prophylaxis versus 18% and 9% without, respectively.

CNS involvement in SCLC not only is a frequent complication, but also its frequency increases with lengthening survival. The necessity of routine use of brain CT scan during staging and follow-up is questioned in view of the present data. Administration of cranio prophylaxis did not reduce the frequency of CNS involvement in our series apparently because while it significantly delays CNS involvement, it does not abolish it. Nevertheless, survival of complete responders was prolonged with cranio prophylaxis and very significantly so in limited disease. This last finding, although clear cut, must await confirmation from randomized trials. The Oncologist 1997;2:153-159

INTRODUCTION

Central nervous system (CNS) metastases are a frequent complication of small cell lung cancer (SCLC) and occur at diagnosis or during the subsequent course of disease. Several reports have been published in the past commenting on incidence, distribution, management, and prognosis of brain metastases in SCLC [1-5]. With only one exception [5], those studies have been published at a time when diagnostic and mainly therapeutic approaches of patients with SCLC were very different from today. On the other hand, despite early suggestions that prophylactic cranial irradiation (PCI) should be part of the treatment of SCLC [6], its exact role is still evolving. We considered it appropriate, therefore, to present the findings of a study we conducted in the Department of Medical Oncology at Evangelismos Hospital, the largest general hospital in Greece.

AIM OF THE STUDY

The aim was twofold: to study the frequency and manifestations of CNS involvement and to assess the role of PCI in patients with SCLC.

PATIENTS AND METHODOLOGY

The population of the study consists of all patients with a confirmed diagnosis of SCLC admitted to our department.

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within the last 15 years. The diagnosis was based on one or more of the following: histology of the biopsy material taken during bronchoscopy, biopsy of a peripheral node/tissue, cytology of fine needle aspiration, sputum cytology, and/or bronchial brushing and lavage.

Staging procedures included: detailed clinical examination, full blood count and erythrocyte sedimentation rate (ESR), liver biochemistry, renal function tests, chest X-rays, CT scan of thorax and abdomen, bone scan, and skeletal survey as indicated. The policy regarding the use of brain CT scan during staging and follow-up varied during the study. Patients were staged as having limited (LD) or extensive disease (ED).

Fairly aggressive polychemotherapy was used. Although minor variations between chemotherapeutic regimens did exist, the basic chemotherapy combination included cyclophosphamide, doxorubicin, and etoposide ± methotrexate. Thirty-seven patients received three cycles of cisplatin plus etoposide alternating with three cycles of the basic regimen (Table 1).

World Health Organization response criteria were used for assessment and characterization of response. According to our therapeutic protocol, PCI was offered to all patients with a documented complete response (CR) immediately after six courses of chemotherapy. Accordingly, this is not a randomized study and complete responders did not receive PCI, either because they denied it or because of residency outside Athens. The irradiation schedule was uniform throughout the study and consisted of whole-brain irradiation at 40 Gy in 20 fractions using a Cobalt-60 machine.

For statistical analysis of the results, $X^2$ test, Kaplan-Meier method, and log rank test were used.

**RESULTS**

The characteristics of the 200 patients studied are shown in Table 2. Median follow-up was 11 months (1-120 months). Eighty-seven patients (43.5%) were followed for more than 12 months.

**CNS Involvement**

In total, 81 patients (40.5%) developed CNS involvement sometime during the course of their disease and in 57 (28.5%) it was the main disease manifestation. Among these 81 patients, seven (9%) were asymptomatic at diagnosis. Table 3A summarizes the findings concerning the timing of CNS involvement, while Table 3B presents comparative data from the literature. Figure 1 gives the actuarial probability of developing CNS metastases and the actual cumulative number of cases with CNS involvement in all patients. An actuarial probability of 57% at 24 months and of 63% at 48 months was found. The actual cumulative numbers of cases, at the same points of time, were 78 and 81, respectively.

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**Table 1. Chemotherapeutic regimens used throughout the study**

<table>
<thead>
<tr>
<th>Chemotherapeutic combination</th>
<th>Schedule</th>
<th>Cycles</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine 2 mg i.v. stat d.1</td>
<td>q.3 wks</td>
<td>6</td>
<td>115</td>
</tr>
<tr>
<td>Doxorubicin 40 mg/m² i.v. stat d.1</td>
<td>q.3 wks</td>
<td>6</td>
<td>115</td>
</tr>
<tr>
<td>Etoposide 100 mg/m² IVI/2 h d1,3,5</td>
<td>q.3 wks</td>
<td>6</td>
<td>115</td>
</tr>
<tr>
<td>Cyclophosphamide 1,000 mg/m² i.v. stat d.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate 200 mg/m² IVI/6 h d.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folinic acid rescue for 48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 1,200 mg/m² i.v. stat d.1</td>
<td>q.3 wks</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>Doxorubicin 45 mg/m² i.v. stat d.1</td>
<td>q.3 wks</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>Etoposide 120 mg/m² IVI/6 h d.1,2,3</td>
<td>q.3 wks</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² i.v. stat d.1</td>
<td>q.6 wks</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>Etoposide 100 mg/m² IVI/6 h d1-5 (alternating with regimen 1 x 3)</td>
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**Table 2. Characteristics of the study population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>200</td>
</tr>
<tr>
<td>Men (%)</td>
<td>176 (81)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>58 (38-76)</td>
</tr>
<tr>
<td>Limited disease (%)</td>
<td>68 (34)</td>
</tr>
<tr>
<td>Extensive disease (%)</td>
<td>132 (66)</td>
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</tbody>
</table>

**Table 3A. Time of CNS involvement**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Main manifestation</th>
</tr>
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<tbody>
<tr>
<td>During staging</td>
<td>20 (10)</td>
</tr>
<tr>
<td>During chemotherapy</td>
<td>14 (7)</td>
</tr>
<tr>
<td>During follow-up</td>
<td>47 (23.5)</td>
</tr>
<tr>
<td>Total number</td>
<td>81 (40.5)</td>
</tr>
</tbody>
</table>

**Table 3B. Comparative data from the literature concerning timing of CNS involvement**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>10%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>During chemotherapy</td>
<td>7%</td>
<td>20%</td>
<td>22.5%</td>
<td>36%</td>
</tr>
<tr>
<td>During follow-up</td>
<td>23.5%</td>
<td></td>
<td>36%</td>
<td>65%</td>
</tr>
<tr>
<td>Total number</td>
<td>40.5%</td>
<td>30%-40%</td>
<td>36%</td>
<td>65%</td>
</tr>
</tbody>
</table>
The findings concerning CNS involvement during staging and follow-up were then separately analyzed according to our policy in the use of brain CT scan. The results are shown in Table 4. During staging, comparison of the findings between 1980 and 1984 when brain CT scan was optional, and between 1985 and 1996 when it was obligatory, demonstrated no significant difference (p > 0.1). During follow-up, no significant difference was found in the period 1985-1991 when brain CT scan was performed systematically every six months and 1992-1996 when it was performed only if clinically indicated (p > 0.1).

The development of CNS metastases in relation to the extent of disease and type of response to chemotherapy is presented in Table 5. No correlation was found with either parameter of disease. The location of CNS metastases was as follows: 66 (33%) were parenchymal lesions, 12 (6%) meningitis carcinomatosa, three (1.5%) spinal cord compression and three (1.5%) diabetes insipidus, in two of whom it was the only manifestation of CNS involvement (Table 6).

**PCI**

The development of CNS metastases in relation to PCI administration, in the 79 patients who achieved CR, is shown in Table 7A. There was no significant difference in the frequency of CNS involvement between PCI receivers and nonreceivers (p > 0.1). On the contrary, the frequency of developing CNS metastases as the sole site of relapse was significantly different between the two groups (p < 0.05). Comparative data from the literature are given in Table 7B. Actuarial development of CNS involvement by PCI receivers and nonreceivers is illustrated in Figure 2. The two curves are not different (p > 0.1).

Finally, the actuarial survival of complete responders who received PCI was compared with that of complete responders who did not (Fig. 3) and a highly significant difference was found (p < 0.001) in favor of PCI receivers. A further comparison of the survival curves, separately for LD and ED (Figs. 4 and 5), demonstrated a significant difference (p < 0.001) only for LD.

**DISCUSSION**

**CNS Involvement**

Although CNS involvement in SCLC is a well-known complication [1, 2, 4, 7, 8], we think our findings add useful information. Overall incidence of CNS involvement found was 40.5%, comparable with the 30%-40% calculated by Pedersen [9] and that reported by others [7, 10-12].
The actuarial curve of developing CNS metastases demonstrated was 57% at 24 months and 63% at 48 months, figures closer to the 50% found in autopsy studies [9, 12]. A tendency to increased probabilities with time has been reported by others [13, 14]. We also found a cumulative number of CNS involvement of 78 at two years and 81 at four years. These findings strongly suggest that the majority of CNS metastases develop during the first 24 months of follow-up and tend to level off after that time. A similar early development of CNS metastases was observed by Maurer and Livingston [14, 15].

During staging, the frequency of CNS involvement did not differ between optional and obligatory use of brain CT scan which raises the question of its necessity as a routine staging procedure. Similarly, during follow-up, no significant difference was found between 1985-1991 when brain CT scan was performed systematically every six months, and between 1992-1996 when it was performed only if clinically indicated. Therefore, in our department, we have adopted the policy of performing brain CT scan during the follow-up only if clinically indicated.

Our finding that 10% of patients had CNS involvement at presentation is similar to that reported by others [9, 13, 16]. Another 7% developed CNS metastases during chemotherapy, 4% as the main manifestation of progression. Pedersen has calculated that CNS metastases development during therapy is of the order of 20% [9], but “during chemotherapy” in our study strictly defines a five- to six-month period. A further 23.5% developed CNS metastases during follow-up, 17.5% as the main manifestation of disease recurrence.

The frequency of CNS involvement found in LD was not different from that found in ED, indicating that ED is not associated with a higher risk of developing CNS metastases. An increased likelihood of CNS involvement at diagnosis in ED was observed by Nugent et al., but was not statistically significant [13]. We were impressed to find no difference in the frequency of CNS metastases between complete and partial responders. In fact, there was a trend toward higher frequency among complete responders. Similar findings have been reported by others [17] and are obviously due to the fact that complete responders, by living longer, are exposed to a higher risk than either partial responders or the general SCLC population [17, 18].

It was not of surprise that cerebral lesions were the most frequent site [12, 13, 19, 20] of CNS metastases, but

<table>
<thead>
<tr>
<th>Table 7B. Comparative data from the literature concerning the frequency of CNS involvement in complete responders with and without PCI</th>
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<tbody>
<tr>
<td><strong>Patients n</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>With PCI</td>
</tr>
<tr>
<td>Without PCI</td>
</tr>
<tr>
<td>Total number</td>
</tr>
</tbody>
</table>

A= present study; B= Cox study [31]; C= Aroney’s study [32]; NR= not reported.

**Figure 2. Actuarial curves of developing CNS involvement in 51 PCI receivers and in 28 nonreceivers.**

**Figure 3. Actuarial survival of 51 CRs who received PCI versus 28 CRs who did not.**
the 6% incidence of meningitis carcinomatosa in our series is higher than reported earlier [16, 21]. Of note, in two autopsy series, the frequency of leptomeningeal metastases was 24% [4, 13]. We would also like to emphasize the fact that in all three cases with pituitary metastases (1.5%) we observed, diabetes insipidus constituted the presenting symptom and in two it was the sole site of CNS involvement. The observed frequency of spinal cord compression is among the lowest reported [4, 12, 13].

**PCI**

Although it is now more than twenty years since the first advocation of PCI in SCLC [6], the debate about its current position in the management of SCLC still continues [18, 22, 23]. There are several reports on the subject based on nonrandomized and randomized trials [14, 24-30], but a review of the literature easily leads to the conclusion that more information is required before the role of PCI in SCLC can be defined. The present findings based on a close follow-up of 79 patients with SCLC who achieved a documented CR after polychemotherapy add some valuable information. Although this is not a randomized study, it contains data which are valid for comparison. The frequency of CNS metastases in the complete responders after PCI, in our series, was not significantly lower than that observed among the complete responders without PCI. Likewise, no significant difference was demonstrated in the actuarial probabilities of developing CNS metastases between the two groups. Although our findings are in accordance with two randomized [29, 31] and two nonrandomized studies [27, 32], they contrast with the findings of other investigators who constantly observed lower numbers of CNS relapses in the PCI receivers [14, 27, 32-34]. This discrepancy cannot be due to an insufficient radiation dose since we used a dose of 40 Gy/20f. More likely, it is due to a prolonged survival of complete responders in our series; namely, 46% and 26% at two and four years, respectively, compared with ~24% and 12% in most other series [14, 17, 30, 32]. Despite the lack of significant difference in the overall frequency of CNS involvement, the chances of CNS metastases being the sole site of disease relapse were significantly higher without PCI than with PCI. This finding underscores the value of PCI in delaying but not abolishing the occurrence of CNS metastases in patients with CR. Some investigators report very low rates of CNS metastases as the sole site of relapse in complete responders without PCI, and this discrepancy is possibly due to a short duration of CR in their series [35]. Among the 36 complete responders who developed CNS involvement in our series, 61% had no other evidence of recurrence at that time.

Undoubtedly, the most interesting finding of our study is the significantly improved survival of complete responders after PCI. Forty-six percent of complete responders with PCI are projected to be alive at two years, while the probability of being alive at the same time interval without PCI is only 18%. While the latter figure is close to the usually reported two-year survival for complete responders [16, 36], a 46% two-year survival is among the highest reported [36, 37]. Our finding of a significantly improved survival with PCI is in sharp contrast with published results from randomized trials [14, 29, 30, 33, 38]. Although it can be argued that the present study was not a randomized one, thus allowing for a possible selection bias, this reason alone could not explain such a big difference in survival. We, therefore, think that the most likely explanation is a difference in disease-free and overall survival between our study and that of others. This probability is supported by: A) the impressively high actuarial survival of complete responders
with PCI in our series; B) the fact that 9 of 11 published randomized trials which failed to demonstrate an improvement in survival with PCI did not take into consideration the type of response to chemotherapy [18]; C) the very low number of isolated CNS recurrences reported by others, and D) the lack of significant difference in the frequency of CNS metastases between complete responders with and without PCI in our study.

Very recently, Rubenstein also reported an improved survival in complete responders with PCI compared with complete responders without PCI. The two-year survival in his series was 46%, identical to ours [36].

Finally, it is worthy of emphasis that the improvement in survival after PCI proved statistically significant only in patients with LD. Improved survival of LD patients has been very recently reported in two other studies [36, 37]. This interesting observation clearly indicates that the stage of disease has to be incorporated into the inclusion criteria of trials investigating the impact of PCI on survival of patients with SCLC. From this point of view, it is of interest that among the four large ongoing randomized multicenter trials of PCI in SCLC being conducted among the membership of IASLC, one recruits patients with limited disease only [18, 39].

Toxicity

No prospective detailed neuropsychological evaluation was included in our study, and subclinical neurological or mild psychological abnormalities cannot be excluded. Nevertheless, no clinically significant short-term or long-term toxicity was observed despite the fact that a number of PCI receivers are still alive after more than five years.

Conclusions

CNS involvement is a frequent manifestation of SCLC, and its frequency is increasing with lengthening survival. A 10% sector of patients has CNS involvement at presentation. Routine use of brain CT scan during staging is of questionable usefulness although its use if clinically indicated during follow-up seems reasonable. ED is not associated with higher incidence of CNS involvement. Complete responders demonstrate a trend in developing CNS involvement more frequently because they live longer. The finding of improved survival of complete responders who received PCI, although clear-cut in our study, must await confirmation from large randomized trials. Until that time, we think it is advisable to offer PCI to all complete responders with limited disease.

References


