Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients

R. Arriagada¹*, T. Le Chevalier¹, A. Rivière², P. Chomy³, I. Monnet⁴, E. Bardet⁵, J. A. Santos-Miranda⁷, C. Le Péchoux¹, M. Tarayre¹, S. Benhamou⁶ & A. Laplanche¹

¹Institut Gustave-Roussy, Villejuif; ²Centre François Baclesse, Caen; ³Fondation Bergonié, Bordeaux; ⁴Centre Hospitalier Intercommunal de Créteil; ⁵Centre René Gauducheau, Nantes; ⁶Institut National de la Santé et de la Recherche Médicale, Unité 521, Villejuif, France; ⁷Hospital Gregorio Marañón, Madrid, Spain

Received 1 June 2001; revised 9 October 2001; accepted 22 November 2001

Background: Prophylactic cranial irradiation (PCI) has a beneficial effect on overall survival in patients with small-cell lung cancer (SCLC) in complete remission as shown in a worldwide meta-analysis. The current analysis aimed to evaluate PCI effects on patterns of failure in this patient category.

Patients and methods: The Institut Gustave-Roussy coordinated two parallel randomized studies including a total of 511 patients with SCLC. Patients were randomly assigned to either PCI (24 Gy in eight fractions and 12 days) or no PCI. Patterns of failure were analyzed according to (i) total event rates and (ii) isolated first site of relapse using a competing risk approach.

Results: Five hundred and five patients were analyzed. The 5-year cumulative rate of brain metastasis as an isolated first site of relapse was 37% in the control group and 20% in the PCI group ($P < 0.001$). The overall 5-year rates of brain metastasis were 59% and 43%, respectively [relative risk (RR) 0.50; $P < 0.001$]. The 5-year overall survival rates were 15% in the control group and 18% in the PCI group (RR 0.84; $P = 0.06$).

Conclusions: PCI decreased significantly the risk of brain metastasis. Other events were not influenced. The relative death risk reduction was of borderline significance. Results reported as isolated first cause of failure and subsequent competing events may explain why a major treatment effect on brain metastases rate has a rather moderate effect on survival.

Key words: brain metastases, competing risks, prophylactic cranial irradiation, randomized trial, small-cell lung cancer

Introduction

Prophylactic cranial irradiation (PCI) in patients with small-cell lung cancer (SCLC) decreases the overall rate of brain metastases, as shown by several randomized trials conducted in the 1970s and 1980s [1–13]. Results from retrospective data suggested a potential benefit on survival restricted to patients in complete remission [14]. Individual trials were, however, unable to detect a significant effect on overall survival. It was necessary to perform an overview based on individual patient data to show a moderate but significant effect on death reduction, with an absolute survival benefit of 5.4% [15].

Another issue on the use of PCI was its possible toxic and deleterious effect on brain function. In the early 1980s, based on retrospective analyses, several authors suggested a possible toxic effect of PCI including neuropsychological syndromes and brain computed tomography (CT) abnormalities [16–26]. The exact significance of these changes was difficult to interpret from the analysis of retrospective series. Specific evaluations performed in two prospective randomized trials, however, failed to show any significant detrimental effect when PCI total doses were equal to or lower than 36 Gy [27, 28].

The two randomized trials reported here were activated in 1985 and in 1988 [29]. The common objective was to evaluate the effects of PCI on brain metastasis and overall survival in patients with SCLC in complete remission. The first trial also evaluated late toxic effects of PCI and results were published in 1995 [27]. The joint analysis of both trials gives the opportunity to analyze the sites of failure of patients for both brain metastases and other sites of tumor progression.

*Correspondence to: Dr R. Arriagada, Instituto de Radiomedicina, Américo Vespucio Norte 1314, Casilla 124, Santiago 34, Chile. Tel: +56-2-206-14-00; Fax: +56-2-228-70-03; E-mail: gocchi@ctcinternet.cl
Patients and methods

Trials design

The first trial (PCI85) activated in 1985 included 300 patients mainly in France (see Acknowledgements for participating organizations). The size of the trial was calculated to show a difference in the brain metastasis rate as first site of recurrence. The trial included a prospective evaluation of neuropsychological functions and morphological alterations by CT scan. The second trial (PCI88) included 211 patients. It was initiated in October 1988 and proposed a simplified protocol (mainly without neuropsychological evaluation) to allow other centers to include patients and increase the statistical power for evaluation of a potential treatment effect on overall survival. It was conducted in European countries (see Acknowledgements), and recruitment was interrupted in 1994 when results of PCI85 were known by trialists. The data collection and statistical analyses for both trials were carried out in the Department of Biostatistics at the Institut Gustave-Roussy.

Inclusion criteria

Patients with histologically confirmed SCLC were eligible for inclusion in these randomized trials if they were considered in complete response after or during induction treatment. In PCI85, complete response was defined as the disappearance of all tumor signs as confirmed by the chest film, and by macroscopic and histological evaluation at the time of fiberoptic bronchoscopy. In PCI88, the definition of complete response was defined by each participating center; it could include an evaluation by a simple chest X-ray. In both protocols, complete response could be obtained by any chemotherapy regimen, with or without thoracic radiotherapy, or surgery. Patients with initially limited or extensive disease were eligible. Limited disease was defined as cancer limited to one hemithorax, the mediastinum, and supraclavicular nodes, provided that all volumes could be included in the same radiotherapy field as the primary tumor. Other eligibility criteria included an age of 70 years or less; Karnofsky performances status over 60%; no history of other cancers (excluding basal cell skin carcinoma); and a brain CT scan without brain metastases. Patients with extensive disease required a complete response at all disease sites. Patients were randomized as soon as complete remission was established to receive either PCI delivering 24 Gy in eight fractions during 12 days, four fractions per week (treatment group) or no PCI (control group). In PCI88, the suggested dose was 24 Gy in eight fractions but it was left to the choice of each participating center, between the following limits: a total dose between 24 and 30 Gy, and a dose per fraction equal or lower than 3 Gy. Maintenance chemotherapy was allowed provided it was not administered concomitantly with PCI.

For radiation treatment, the target volume was the whole brain. Treatment was delivered by a photon beam with energy >1 MV, through two opposed lateral fields with shielding of the ocular globes. The temporal fossa should be within the fields; the lower margin of the fields was in the cervical spine C2–C3. Dose was specified at the beam axis according to the International Commission of Radiation Units and Measurements recommendations [30]. Simulator film and individual blocks were recommended and verification of portal films was mandatory.

The local committees of participating hospitals according to current French or European regulations approved the studies, and patients gave informed consent to participate.

Other treatments

Corticosteroids were given during treatment only if the patient developed side-effects such as headache or vomiting. Concurrent chemotherapy during PCI was not allowed and a 1-week interval was requested before and after radiation treatment. After a recurrence other than the brain, the recommended salvage treatment was the one usually given in each center. Only for isolated brain metastases, the following recommendations were given by the protocol: brain irradiation at a dose of 50 Gy in 28 fractions for patients in the control group and 39 Gy in 22 fractions for patients in the PCI group.

Follow-up

Patients were followed every 6 months clinically and radiologically at the thoracic level. Brain CTs (other than those systematically specified in PCI85) and other systemic assessment were requested according to clinical signs or symptoms. The median follow-up was 11 years [31]. Neuropsychological assessment was only done in the PCI85 trial, as previously reported [27].

Statistical analyses

A centralized telephone-call procedure was used to assign patients randomly to treatment groups, and allocations to each group were made from a computer-generated list stratified according to center, once eligibility criteria had been verified.

The main end points were the occurrence of brain metastasis and overall survival.

Demographic and clinical characteristics were compared by the chi-square test and by Student’s t-test. All event time occurrences were calculated from the date of randomization to the date of the event or to the last follow-up visit. The Kaplan–Meier method [32] and Rothman’s 95% confidence interval [33] were used to estimate survival and event-free survival. The log-rank test [34] was used to compare the two groups for differences in survival and overall event-free rates. The log-rank test was also applied to each cause-specific event, ignoring all other events (only death as first event censored the occurrence of other events). Relative risks for this method were calculated from the ratio of observed to expected number of events for the whole follow-up period.

For the study of the pattern of failure and brain metastasis rate, a model assuming competing risks was used [35, 36]. This approach includes all events defining relapse by using cumulative incidence functions to estimate event-specific rates. These incidence estimates subdivide into separate components, which add up to the overall event rates. No assumption of independence between event types is necessary. In this context, events are considered as competing risks and the appearance of one type of event does not censor the appearance of another. Event-specific cumulative incidence curves were estimated from the decomposition of the event-free survival curves, and a computer program (COMPETE) developed at the Institut Gustave-Roussy [37, 38] was used for the calculations. These rates were compared using a test developed by Gray [39]. Analyzed events included isolated brain metastasis, other distant relapses including second cancers, local recurrence and death. Event rates obtained by this method are reported as first site of relapse. All analyses were conducted on an intention-to-treat basis.

Results

Clinical findings

From May 1985 to March 1993, the 300 planned patients were enrolled at 19 centers in PCI85. One hundred and forty-five patients were assigned to the PCI or treatment group and 149
to the control group. From October 1988 to April 1994, 211 patients were enrolled at 24 centers in PCI88 [40], 100 were assigned to PCI and 111 to the control group.

In PCI85, 13 patients did not meet the inclusion criteria: seven in the treatment group (four with brain metastases, two with other metastases and one with uncontrolled thoracic disease at the time of randomization) and six in the control group (two with brain metastases, one with other metastases, one with uncontrolled thoracic disease at the time of randomization, and two with history of another cancer). Only the six patients with brain metastasis at the time of randomization were not included in the analysis because PCI was not applicable. In PCI88, one patient in the treatment group did not meet the inclusion criteria, as he had liver metastases at the time of randomization.

The demographic and clinical characteristics of the patients are shown in Table 1. There were no significant differences between the two groups in any of these characteristics.

### Primary treatment

As shown in Table 1, the mean time between initiation of the primary treatment and randomization was 5 months. About 83% of patients presented with limited disease. All patients with extensive disease had initially distant metastases. In PCI85, 92% of patients received thoracic radiotherapy before randomization, and 99% received chemotherapy including cyclophosphamide, doxorubicin, etoposide and cisplatin [35]. In PCI88, the details of treatments preceding randomization were not registered [40].

### Compliance

In PCI85, among the 145 analyzed patients of the treatment group, three died before treatment and one secondarily refused the treatment. Among 141 patients who actually received PCI, 126 (89%) were administered with the prescribed total radiation dose of 24 Gy, eight (6%) had a total dose of 30 Gy and seven other patients were delivered radiation doses either less than 24 Gy or not higher than 34 Gy. Among 149 patients of the control group, one patient received the treatment by mistake.

In PCI88, six patients did not receive PCI in the treatment group and two patients were treated in the control group. Eighty-one percent of patients in the treatment group received the recommended dose of 24 Gy in eight fractions and 14% a dose of 30 Gy in 10 fractions.

#### Brain metastasis rate and event-free survival

The median follow-up was 11 years. All brain metastases appeared within the first 2 years. Results in terms of brain metastasis as an isolated first site of relapse using competing risk methodology are shown in Figure 1. The 5-year isolated brain metastasis rates were 37% in the control group and 20% in the treatment group ($P < 0.001$). Other recurrences and causes of failures are shown in Table 2.
Overall survival and event-free survival

Overall survival is shown in Figure 2. The 3- and 5-year survival rates were 18% and 15% in the control group, and 26% and 18% in the treatment group. The relative risk of death was 0.84 (P = 0.06).

Event-free survival is shown in Figure 3. The 3- and 5-year rates were 15% and 11% in the control group, and 20% and 17% in the treatment group, respectively. The relative risk of death or event was 0.73 (P = 0.001).

First and subsequent events

The results in terms of isolated brain metastases, other first events and subsequent events are summarized graphically in Figure 4.

Discussion

PCI given to patients with SCLC in complete remission significantly decreased the risk of developing brain metastases. This effect was the same whether total brain metastasis or brain metastasis as the first site of failure was used in the assessment. Other events were not influenced by treatment. The effect of treatment on overall survival was not significant, but the relative death risk reduction (0.84) was similar to that observed in the meta-analysis [15], but of borderline significance (P = 0.06).

None of the published randomized trials on PCI [13] showed an effect on overall survival. This effect poses a major question for adjuvant local treatments. In general, this effect is moderate in spite of a major local effect. For example, thoracic radiotherapy decreases three-fold the risk of local recurrence in limited SCLC, but its effect on overall survival is at the

Table 2. Five-year event rates after randomization in two trials comparing prophylactic cranial irradiation (treatment) with absence of treatment (control) for patients with small-cell lung cancer in complete remission

<table>
<thead>
<tr>
<th>Event</th>
<th>First event only (competing approach)</th>
<th>Total events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (n = 245)</td>
<td>Control (n = 260)</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>20%</td>
<td>37%</td>
</tr>
<tr>
<td>Other metastases</td>
<td>32%</td>
<td>26%</td>
</tr>
<tr>
<td>Thoracic relapse</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Intercurrent death</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Total events</td>
<td>83%</td>
<td>89%</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Relative risk (RR) of the treatment group compared with the control group.

**Gray test.

***Log-rank test.

Figure 2. Overall survival in patients with small-cell lung cancer, according to treatment group (P = 0.06, log-rank test). PCI, prophylactic cranial irradiation.

Figure 3. Event-free survival according to treatment groups (P = 0.001). PCI, prophylactic cranial irradiation.
level of 5–6% at 3 years, as shown in a worldwide meta-analysis including more than 2000 patients [41]. In the present study, PCI decreased the risk of brain metastases two-fold. The effect on survival was not significant but it suggests a mortality reduction of 14%. This effect would be independent of that provided by thoracic radiotherapy, as most patients already received this treatment, and thus, their effects could be added. A PCI overview including seven randomized trials and 987 patients was reported [15] and showed a significant mortality reduction of 14%, with an absolute benefit on overall survival of 5.4% at 3 years, similar to the benefit demonstrated for thoracic radiotherapy.

The current study focused on patterns of failure in a large prospective series of 505 patients. In the control group, from 96 patients who developed isolated brain metastases as first event, 31 had another recurrence later. Respective numbers in the treatment group were 49 and 11. Patients free of events, including death, were 18 in the control group and 29 in the treatment group. The study of isolated brain metastases and of subsequent events is shown in Figure 4. In summary, in the control group, 37% of patients developed isolated brain metastasis compared with 20% in the treatment group. From these patients, 12% and 4.5% developed a subsequent tumor event, respectively. Taking into account all brain metastases, only 41% and 57% were free of this event, respectively (Table 2). If other events are taken into account, however, at the end of follow-up only 7% and 12% of these patients are free of events. This difference is well expressed by the 5-year event-free survival, 11% and 17%, respectively. This rather small difference corresponds to the proportion of patients who could benefit from PCI in terms of overall survival and is nearer to the total survival gain observed in the meta-analysis (between 5% and 6%). This kind of analysis was not conducted in the overview material, as information was not available in all trials regarding subsequent failures after the first recurrence.

In the current trials, patients were followed by clinical and brain CT scans. It could be argued that a regular magnetic resonance imaging examination could have detected small brain metastases and that earlier treatment could allow for comparable results in the control group. Until now, however, a curative effect for brain treatment has not been demonstrated for patients with overt metastases [42].

In conclusion, our results confirm the beneficial PCI effect on brain metastasis rates and are consistent with a moderate beneficial effect on overall survival. The analysis of brain metastasis as isolated first cause of failure and subsequent competing events may explain why a major treatment effect on brain metastasis rate translates to a moderate effect on survival.

Acknowledgements

Supported in part by a grant 883063 from the Institut National de la Santé et de la Recherche Médicale/Caisse Régionale d’Assurance Maladie, d’Ile de France, France. Participants in the PCI85 trial were: Institut Gustave-Roussy, Villejuif (R. Arriagada, P. Baldeyrou, S. Benhamou, J.-J. Brelet, P. Girard, T. Le Chevalier, P. Ruffié, M. Tarayre, A. Tardivon); Hôpital St Joseph, Paris (F. Borie); Centre François Baclesse, Caen (A. Rivière); Centre Hospitalier Universitaire, Caen (F. Via- dier); Fondation Bergonié, Bordeaux (P. Chomy); Centre Hospitalier Intercommunal, Crèteil (H. de Cremon, M. Martin, I. Monnet); Clinique de Clermont-Ferrand (A. Tourreau); Hôpital A. Becle, Clamart (M.-C. Cerrina, R. Metrau); Centre A. Laccassagne, Nice (J. L. Lagrange); Hôpital Pitié Salpêtrière, Paris (B. Dautzenberg); Hôtel Dieu, Paris (B. Lebeau, J.-M. Brechot); Hôpital St Quentin (T.-N. Quang); Hôpital Salvador, Marseille (J.-P. Kleibauer); Centre Hospitalier Universitaire, Limoges (B. Roulet); Centre René-Huguenin, St Cloud (P. Rambert); Hôpital de Corbeil, Corbeil, (J.-C. Saltiel); Hôpital Laennec, Paris (C. Delaisements); Hospice Civil, Strasbourg (E. Quioix); Centre Léon-Berard, Lyon (P. Rebattu); Centre Hospitalier Emile-Roux, Eaubonne (P. Dournovo), all in France, and Clínica Privada de Radioterapia, Córdoba (S. Zunino), Argentina. Participants in the PCI88 trial were: Centre Hospitalier Intercommunal, Crétel (I. Monnet); Institut Gustave-Roussy, Villejuif, after March
References


