Prophylactic Cranial Irradiation in Small-Cell Lung Cancer: Is It Ever Indicated?

By Anna Gregor, MD, FRCP [2]

Prophylactic cranial irradiation (PCI) is being reintroduced into multimodality treatment protocols of patients with small-cell lung cancer (SCLC). The history of its use brings interesting insights into clinical evaluations of treatment strategies and design of relevant and informative trials. The critical issues of effectiveness and overall health gains of prophylactic cranial irradiation have been addressed in a series of recently completed clinical trials. These trials tested prophylactic cranial irradiation in small-cell lung cancer patients achieving good response to induction therapy and confirmed the ability of standard prophylactic cranial irradiation schedules to significantly reduce the lifetime risk of brain metastases. A subset of these trials evaluated neurotoxicity in a formal and prospective manner. No sustained or significant detriment in neuropsychometric function could be linked to the use of prophylactic cranial irradiation. In addition, all the large trials have shown a consistent survival advantage in favor of the prophylactic cranial irradiation arm. None of the individual sample sizes were large enough to statistically confirm this survival benefit, but a meta-analysis is in progress and will report on this aspect of evidence shortly. Issues that remain to be answered are the optimal dose and schedule of prophylactic cranial irradiation as well as the timing of this administration. These questions form the nucleus of the next generation of collaborative trials that are being designed.[ONCOLOGY 12(Suppl 2):19-24, 1998]

The practice of clinical medicine is more often art than science and, as such, is prone to both subjective and personal interpretations in addition to analytic and objective evaluation of available evidence. The increasing difficulties of introducing evidence-based medicine into clinical practice testify both to the individualism of the medical profession and to the problems of relating conclusions derived from patient populations to decisions about the management of individuals. These observations help to explain the varying fortunes and acceptance of novel treatment interventions. The use of prophylactic cranial irradiation (PCI) to prevent or delay brain metastases in small-cell lung cancer, a disease with a high incidence of involvement at this metastatic site, is one such example.

Early Experience With Cranial Irradiation

Pediatric Oncology
In the late 1960s, prophylactic cranial irradiation was found to be effective in reducing relapse rates and improving survival for patients with acute lymphoblastic leukemia (ALL).[1] Now, however, prophylactic cranial irradiation has all but disappeared from the treatment protocols for this disease. The reasons for the stepwise, gradual withdrawal of prophylactic cranial irradiation from this setting were twofold: First, concerns that it might cause neurotoxicity in this curable population of children were confirmed; even low-dose prophylactic cranial irradiation with associated reduced effectiveness was found to lead to intellectual detriment on neuropsychometric testing. Second, these findings were accompanied by the development of new, effective alternatives to prophylactic cranial irradiation, in the form of modifications of chemotherapy regimens. As is usual in pediatric oncology, this change of practice was achieved through a number of sequential and controlled steps and evaluated in large-scale clinical trials. This is an unusual example of evidence-based medicine in practice. Unfortunately, adult oncology has never been able to emulate the discipline of its pediatric cousin in complying with this type of clinical-evidence evaluation.

Prophylactic Cranial Irradiation in SCLC
The story of prophylactic cranial irradiation in small-cell lung cancer is a common example of the more intuitive and tortuous methods for determining clinical practice.

Rationale for Introducing PCI
The reasons for the introduction of prophylactic cranial irradiation
in the treatment of small-cell lung cancer are similar to those for acute lymphoblastic leukemia: Brain metastases are a common and cumulatively increasing site of failure. Twenty percent of small-cell lung cancer patients present with central nervous system involvement, 50% develop symptomatic brain metastases by 2 years, and almost all have central nervous system involvement at postmortem.[2-4] Treatment of symptomatic brain metastases is unsatisfactory; only about half of patients achieve a useful palliation,[5] and median survival is less than 3 months.[6] The impact of brain metastases, on socioeconomic issues and on quality of life of patients, is significantly worse than the impact of failure at other metastatic sites,[7] with patients spending prolonged time in hospitals and suffering loss of independence. In this setting, the prevention of brain metastases becomes desirable.

In a chemotherapy- and radiotherapy-sensitive disease like small-cell lung cancer, the reasons why brain metastases remain such a problem are not fully understood. We know that the brain is a site of preferential involvement for all types of lung cancer,[8] and the close relationship between small-cell lung cancer growth and the number of neuropeptides may increase the likelihood of brain as a favored site for small-cell lung cancer metastases.[9] A physical or pharmacologic blood-brain barrier limits access into brain for most water-soluble drugs,[10] and small-volume tumors have not yet developed the tumor-associated vasculature that allows chemotherapy access to established and contrast-enhancing metastases. In light of all these problems, the effectiveness of prophylactic cranial irradiation in the management of brain involvement in acute lymphoblastic leukemia looked promising and suggested its application in small-cell lung cancer.

**First Trials in SCLC** The first wave of trials of prophylactic cranial irradiation in small-cell lung cancer was completed in the 1970s and early 1980s.[11-20] The results of those studies confirmed a significant reduction in the incidence of brain metastases following prophylactic cranial irradiation (Table 1). This did not translate, however, into a demonstrable survival benefit. The patient populations had a variable distribution of prognostic factors, such as disease extent and response to induction chemotherapy. Because any advantage in response duration and survival attributable to prophylactic cranial irradiation was likely to be small, it could have been lost among the more powerful determinants. The ability to detect such small differences would have been further impaired by the small sample size, given that individual trials included between 30 and 250 patients, and only three studies had more than 100 randomized patients.[15,19,20]

**Specter of Neurotoxicity** The feature that caused major concern was neurotoxicity. Disturbing numbers of long-term survivors of small-cell lung cancer were found to have variable degrees of dementia and radiologic abnormalities of the brain.[21-23] Most, but not all, had received prophylactic cranial irradiation as a part of their treatment. Given that all these reports were based on retrospective or recall evaluation of selected groups of patients, no formal relationship between the likely predisposing causes could be studied. As a well-recognized cause of central nervous system toxicity,[24] prophylactic cranial irradiation was likely to play a role, but the assumption that it was the sole culprit could not be supported from the available evidence. Nevertheless, prophylactic cranial irradiation was banned from most multidisciplinary protocols and an active search for alternative strategies began.

**Recent Experience**

The realization that chemotherapy alone will not prevent central nervous system disease[25,26] led to a new wave of trials involving more than 1,000 small-cell lung cancer patients[27-30]. Most of these patients had limited disease and good responses to induction chemotherapy. In addition, in most cases, prophylactic cranial irradiation was delivered at the time of remission, thus avoiding postradiation chemotherapy, which is known to potentiate neurotoxicity. Prophylactic cranial irradiation doses were between 24 and 36 Gy, given in 2- to 2.5-Gy fractions. Of these modern studies, three large ones (approximately 300 patients each) have been completed and reported in the last 18 months.[27-30] Two of these, CPH and UK02, incorporated prospective neurologic and neurofunctional assessment in their designs.[27,29]

**CPH Trials**

The two French collaborative trials, PCI 85 and PCI 88, ran parallel.[27,28] Both were randomized trials of prophylactic cranial irradiation and controls, but PCI 85 required a fixed dose of 24 Gy in eight fractions, whereas PCI 88 allowed institutional choice of radiation schedules, but 76% of patients received 24 Gy in 8 fractions (Table 2). As reported at the 1995 European Cancer Conference (ECCO),[28] the radiation arm had a highly significant reduction in brain metastases (overall, from 59% to 40%, $P < .0001$; isolated, from 57% to 39%, $P < .0001$). Both trials have shown...
a trend for survival benefit of PCI, which did not reach statistical significance (RR, 0.85; \( P = .1\)). The PCI 85 trial included a prospective neurologic evaluation that showed a low and clinically insignificant rate of radiologic abnormalities on computerized tomography, but no evidence of dementia or serious central nervous system morbidity.

**UK02 Trial**

The UK02[29] trial was initially designed as a three-arm randomized study to compare two dose levels of prophylactic cranial irradiation (24 Gy and 36 Gy in 2-Gy fractions) vs a control arm (no prophylactic cranial irradiation). In the first 3 years, only 100 patients were randomized and the trial was relaunched as a two-arm study, allowing investigators at the participating institutions a choice of prophylactic cranial irradiation schedules. A total of 40% of patients received 30 Gy in 10 fractions, but schedules from 8 Gy in single fractions to 36 Gy in 18 fractions were used.[29] It also incorporated prospective neuropsychometric assessment for all patients recruited at three of the participating institutions. Intake picked up and the trial closed in May 1995, exceeding its target with 314 randomized patients.

The eligibility criteria, which remained the same throughout, comprised limited-disease patients who achieved remission following induction chemotherapy. Patients were randomized within 4 weeks of response assessment. No planned postprophylactic cranial irradiation or concurrent chemotherapy was allowed, although concurrent chest irradiation could be performed in the patients randomized to receive prophylactic cranial irradiation.

**Results** The trial confirmed the effectiveness of prophylactic cranial irradiation in reducing the rate of brain metastases. At 2 years follow-up, 52% of the control group vs 29% of prophylactic cranial irradiation-treated patients failed in the brain (Figure 1). [Hazard ratio 0.41(95% CI, 0.27 to 0.63), \( P = .0002 \)].

Interestingly, among the first 100 patients randomized, the advantage was seen only at the higher prophylactic cranial irradiation dose level (36 Gy in 18 fractions): hazard ratio 0.16 (95% CI, to 0.07 to 0.36). Patients receiving lower dose level (24 Gy in 12 fractions) behaved like the control patients. [Hazard ratio 0.71 (95% CI, 0.36 to 1.43)]. The French trials also used 24 Gy, but in 8 rather than 12 fractions; [27,28] it is possible that low-dose prophylactic cranial irradiation schedules require increased fraction size.

**Dose-Response Relationship** The relationship between risk of brain relapse and prophylactic cranial irradiation schedule in the UK02 trial can be seen in Figure 2. The radiation schedules have been converted into a biologically equivalent dose at 2 Gy (BED), using a linear quadratic model and coefficient for acutely reacting tissues or tumor.[31] The confidence intervals on some of the schedules are large because only a few patients received them, but for the randomized comparisons and the majority of patients who were treated with 30 Gy in 10 fractions, the relationship appears linear.

This demonstration of a dose-response relationship in small-cell lung cancer is a useful contribution to the overall evidence of radioresponsiveness in this disease, and it is the first time a relationship between radiation dose and local control could be seen in the setting of brain metastases. It now needs to be confirmed in a larger randomized trial, which also should try to determine whether the size of the total radiation dose can be at least partially compensated by increasing the individual fraction size. This approach may be considered risky, as large fraction sizes have been thought to predispose to increased levels of central nervous system toxicity.[32]

**Neuropsychometric Testing in the Uk02 Trial**

What is the toxicity evidence from the one trial that did incorporate formal neuropsychometric testing into its design? First of all, it is possible to test a number of domains of intellectual function using specially trained personnel, but not necessarily qualified psychologists.

**Tests of Cognitive Function**

Three contributing institutions in the UK02 study recruited 136 patients who were assessed using the following tests of cognitive function: The National Adult Reading Test[33,34] was applied pretreatment, once only. The Rotterdam Symptom Checklist,[35] to which had been added items on cognitive function from the Sickness Impact Profile;[36] the Hospital Anxiety and Depression Scale;[37] the Paced Auditory Serial Addition Task;[38] the Rey Osterrieth Complex Figure Test;[39] and the Auditory Verbal Learning Test[40] were applied at each assessment. These are all standard quality of life and neuropsychometric tests and have validated age-related norms.

The National Adult Reading Test, in which the patient is asked to read lists of words with variable degrees of common usage and complexity, is a method of assessing premorbid intellectual function.
The Rotterdam Symptom Checklist is a brief questionnaire covering physical symptoms, activities of daily living, and psychological distress. The Hospital Anxiety and Depression Scale is a screening scale for anxiety- and depression-impaired performance on neuropsychologic testing.[37] In the Paced Auditory Serial Addition Task, the patient hears a taped presentation of digits at constant speed and is asked to add each number to the previous one. In the Rey Osterrieth Complex Figure Test, the patient is asked to copy and later draw from memory a complex figure. In the Auditory Verbal Learning Test, the patient is asked to memorize word lists.

In summary, these tests are used to assess quality of life, performance status, activities of daily living, psychological distress, auditory mental tracking, perceptual organization, visual memory, memory span, and verbal learning. Therefore, they can be used to evaluate various aspects of quality of life and cognitive efficiency.

**Results of Cognitive Function Tests** Assessments were performed at randomization and every 6 months thereafter. Impairment was defined using standard deviations from age-matched normal controls. At baseline, up to 40% of patients showed significantly abnormal performance on individual tests. Impairment was not related to age, gender, previous therapy, or center and was distributed evenly between the prophylactic cranial irradiation and control arms. Before prophylactic cranial irradiation, 10% of patients randomized to the prophylactic cranial irradiation arm were impaired on more than two tests, compared with 2% of controls.

At 6 months, 59 of 105 evaluable patients were tested and impairment was seen in 41% on the Auditory Verbal Learning Test, 29% on the Paced Auditory Serial Addition Task, and 23% on the Complex Figure test. No significant differences were detected between prophylactic cranial irradiation-treated patients and controls, and similar numbers (20%) of patients in each randomized group showed improvement, as well as no deterioration. The majority of patients remained stable.

One of the major problems in this type of study is the increasing attrition due to relapse, both inside and outside of the brain, thus reducing the number of patients available for study and capable of being tested.[41] This may bias results by preferentially selecting patients who remain well and intellectually able. Unfortunately, this appears unavoidable in a population with an overall median survival of about 12 months following randomization. Continuing neuropsychometric surveillance of all long-term survivors is necessary in order to be certain of the frequency and magnitude of treatment-induced intellectual deficit. However, from the practical point of view, this may not affect the majority of patients, who relapse from their disease long before toxicity manifests itself.

**Other Causes of Impairment**
During the early follow-up relevant to the majority of patients in the UK02 trial, no significant or sustained deterioration of intellectual function was seen. This, together with the finding of impairment of performance in up to 40% of patients before prophylactic cranial irradiation, confirms the findings of Komaki [42] and suggests that factors other than cranial irradiation may play a part in the pathogenesis of the dementing syndromes characteristically associated with small-cell lung cancer. It has been shown previously in a large group of long-term survivors[42,43] that this detriment is not universal and does not adversely affect quality of life and functional ability.

**Conclusions**
The effects of prophylactic cranial irradiation on survival are being investigated by current meta-analysis (personal communication, Dr. Jean Pignon, August 1997) and should become available shortly. Whether the results of this investigation confirm the reproducible but not statistically significant survival difference demonstrated in the UK02 trial (Figure 3) and seen consistently in all the recent trials,[27-30] it is clear that prophylactic cranial irradiation is a practical, useful, and apparently safe method of reducing the risk of brain relapse in patients with small-cell lung cancer. The next generation of trials should address the question of optimal radiation dose and schedule, as well as the role of low-dose prophylactic cranial irradiation as prophylactic palliation in patients with poorer prognosis who have had a good response to palliative chemotherapy. Outside of clinical trials, we should avoid concurrent or postirradiation chemotherapy. Current evidence suggests that 36 Gy in 2-Gy fractions is the most effective regimen for patients who are likely to survive for prolonged periods.

Thus, a treatment first advocated 20 years ago has returned to clinical use. Its journey outlines the often complex and difficult evaluation of patchy clinical evidence and the necessity for revisiting the field and gathering facts afresh from time to time.
References:


Source URL:

Links:
[1] http://www.diagnosticimaging.com/review-article