Does prophylactic cranial irradiation reduce the incidence of brain metastases in extensive small-cell lung cancer?

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A phase III study has shown that prophylactic cranial irradiation decreases the risk of symptomatic brain metastases and may improve overall survival for patients with extensive small-cell lung cancer and response to systemic chemotherapy.

Brain metastasis is a major cause of morbidity and mortality in patients with small-cell lung cancer. Prophylactic cranial irradiation (PCI) is used to treat microscopic or subclinical metastases that are protected from cytotoxic drugs by the blood–brain barrier. Since the 1970s, many trials have evaluated the role of PCI in patients with small-cell lung cancer, but have produced inconclusive results regarding survival benefit.

In 1999, Aupérin et al. conducted a meta-analysis of seven trials that included 987 patients who were in complete remission after chemotherapy for small-cell lung cancer (86% had limited disease), in order to assess the efficacy of PCI.[1] This study showed a 5.4% higher three-year survival rate (20.7 % in the PCI group vs 15.3% in the control group), longer disease-free survival and lower cumulative incidence of brain metastasis in patients treated with PCI compared with controls. According to the analysis of the four total doses (8 Gy, 24–25 Gy, 30 Gy and 36–40 Gy), larger doses of radiation led to greater decreases in the risk of brain metastases.[1]

Slotman and colleagues performed a phase III study to address the role of PCI in patients with extensive small-cell lung cancer who showed any response to 4–6 cycles of systemic chemotherapy (see opposite). The PCI and control groups (each with 143 patients) were well balanced with regard to baseline characteristics. The cumulative risk of brain metastases within one year was 14.6% in the PCI group compared with 40.4% in the control group. PCI was associated with a higher median disease-free survival (14.7 weeks compared with 12.0 weeks in the control group), longer median overall survival from randomisation (6.7 months vs 5.4 months), and a higher one-year survival rate (27.1% vs 13.3%).

In this study, brain imaging was not performed before randomisation unless symptoms indicative of brain metastases were present. Published data indicate, however, that approximately 13% of patients with small-cell lung cancer have asymptomatic brain metastases at the time of diagnosis.[2] Such patients would require a therapeutic dose of radiation (generally 35 Gy in 14 fractions) rather than a lower dose in the range used for PCI.

Conventional wisdom suggests that PCI would not provide survival benefit in patients who have uncontrolled disease at

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the primary or distant metastasis sites, or both, because of the likelihood of reseeding to the brain after such treatment. Slotman and co-workers, however, demonstrated survival benefit of PCI in a setting where the majority of patients had persistent disease at the primary (76%) and/or distant (71%) sites.[3]

Consistent with previous trials of PCI,[4] no difference was found in cognitive functioning or global health status among the two study arms after short-term follow-up; however, fatigue and hair loss adverse events were reported significantly more often by patients in the PCI arm.

Most patients received PCI at a dose of 20 Gy in five fractions in order to minimise the length of treatment. To improve the therapeutic ratio of PCI, it is reasonable to use a standard fractional dose of 2 Gy for a total dose of 30–34 Gy in patients with a good performance status and a complete response to systemic chemotherapy.[5]

Overall, this study provides good evidence that PCI is beneficial for patients with extensive small-cell lung cancer and any response to systemic chemotherapy.

References

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Synopsis

B Slotman, C Faivre-Finn, G Kramer et al. (2007) **Prophylactic cranial irradiation in extensive small-cell lung cancer.** *N Engl J Med 357:664–672*

Background. Brain metastases are common in patients with small-cell lung cancer and indicate a poor prognosis. The role of prophylactic cranial irradiation (PCI) in patients at high risk for symptomatic brain metastases who do not experience a complete response to chemotherapy is unclear.

Objective. To determine whether PCI can reduce the incidence of symptomatic brain metastases in patients with extensive small-cell lung cancer.

Design. In the period February 2001 to March 2006, this randomised, multicentre, phase III trial enrolled 286 patients with histologically or cytologically confirmed extensive small-cell lung cancer. All patients had to have experienced a response to chemotherapy in order to be eligible. Specific inclusion criteria included age between 18 and 75 years, WHO performance status of 0 to 2, response following 4–6 cycles of chemotherapy, no evidence of brain metastases, no previous radiotherapy to the head or neck, and no other cancer.

Intervention. Patients were randomly assigned to undergo PCI (n=143) or to receive no therapy (n=143). Radiation was specified to the midline and delivered on a schedule of 4–5 fractions per week using one of the following schedules: 20 Gy in 5 or 8 fractions; 24 Gy in 12 fractions; 25 Gy in 10 fractions; or 30 Gy in 10 or 12 fractions. Radiotherapy had to commence 4–6 weeks after chemotherapy. When any symptoms indicative of brain metastases were present, CT or MRI was performed.

Outcome measures. The primary outcome was the development of symptomatic brain metastases. Secondary outcomes included survival, toxic effects, quality of life and treatment costs.

Results. Symptomatic brain metastases were observed in 24 patients in the treatment group and in 59 patients in the control group. For the irradiation group, the hazard ratio for symptomatic brain metastases was 0.27 and the cumulative risk of metastases was 4.4% at six months and 14.6% at 12 months. The corresponding cumulative risks in the control group were 32% and 40.4%, respectively. Median survival without disease progression in the irradiation group was significantly longer than that in the control group, (14.7 vs 12 weeks; P=0.02) and median overall survival was significantly longer in the irradiation group than in the control group (6.7 vs 5.4 months; P=0.003). Survival rates at one year were 27.1% and 13.3% in the irradiation and control groups, respectively. Acute reactions associated with irradiation included headache, nausea and vomiting, fatigue and skin reactions.

Conclusion. The incidence of symptomatic brain metastases is reduced after PCI in patients with extensive small-cell lung cancer who have experienced a previous response to chemotherapy.

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