COUNTERPOINTS

Current Controversies in Hematology and Oncology

Should All Patients With SCLC Receive Prophylactic Cranial Irradiation If They Have Responded to Treatment?

Brain metastases are common in patients with small cell lung cancer (SCLC), and prophylactic cranial irradiation (PCI) has been shown to reduce the risk of brain metastases in these patients. But how great are the benefits, and do the benefits outweigh the toxicity? In this month's Counterpoints, Dr Ben J. Slotman makes the case for the use of PCI in nearly all patients with SCLC who have responded to treatment, whereas Jacob Yousef and Dr Henry Wagner argue that the role of PCI should be reassessed.

PCI Should Be Offered in Nearly All Cases

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Brain metastases are detected in approximately 20% of patients with small cell lung cancer (SCLC) at diagnosis, 40% of patients 1 year after diagnosis, and 80% of patients at autopsy. Prophylactic cranial irradiation (PCI) has been shown to reduce the risk of brain metastases in patients with SCLC.

Efficacy in Limited-Stage and Extensive-Stage SCLC

In a meta-analysis of patients with limited-stage SCLC (LS-SCLC) who had complete remission after chemotherapy, PCI reduced the risk of brain metastases from 59% to 33%.[1] This meta-analysis further showed a survival benefit of approximately 6 percentage points at 3 years with PCI vs without (21% vs 15%, respectively). An international randomized trial detected no improvement in outcome with higher PCI dose,[2] and 25 Gy in 10 fractions remains the standard dose for PCI.

PCI also was investigated in patients with extensive-stage SCLC (ES-SCLC), in whom the risk of brain metastases is even higher. A randomized study carried out by the European Organisation for Research and Treatment of Cancer (EORTC) showed that PCI reduced the risk of brain metastases at 1 year from 40% to 15%.[3] In addition, PCI improved overall survival (OS). Survival at 1 year was 27% for patients who received PCI and

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The Time Has Come to Improve On a Former Standard

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SCLC makes up 13% of lung cancers and is characterized by rapid growth and early metastasis.[1] Brain metastases are common, with a 10% prevalence at presentation and a greater than 50% incidence within 2 years of diagnosis, with about half of these appearing limited to the brain.[1,2]

PCI to protect the pharmacologic sanctuary of the central nervous system (CNS) in SCLC was proposed based on its effect in pediatric acute lymphoblastic leukemia (ALL).[1] Early trials comparing PCI with observation showed reduced brain metastases, but inconclusive effects on OS. Aupérin and colleagues conducted a meta-analysis of 7 randomized trials comparing PCI with observation for patients in complete remission after initial treatment. PCI reduced the incidence of brain metastases at 2 years from 58.6% to 33.3% and improved 3-year OS from 15.3% to 20.7%.[3] Meert and colleagues confirmed an OS benefit for those with a complete response, but not if PCI was given at initiation of chemotherapy or to patients with a partial response.[4] For the last 15 years, PCI has been recommended—based on these analyses—for patients with LS-SCLC responding to therapy for intrathoracic

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13% for control patients.[3] PCI was well tolerated, and the negative effect on quality of life (QOL) was limited and only transient.[4] Patients in the PCI arm of the study also were more likely to receive second- or third-line chemotherapy when their disease progressed (68% vs 45%), possibly because they were better able to tolerate chemotherapy in the absence of brain metastases. Virtually all patients who developed brain metastases also developed extracranial progression. The low rate of brain metastases in ES-SCLC after PCI was confirmed in a more recent trial of thoracic radiotherapy.[5]

Concerns About the Use of PCI

If PCI is so effective in reducing brain metastases and improving survival, what are the concerns about its use?

First, PCI may negatively influence cognition.[6] Important risk factors for cognitive decline after PCI are advanced age, diabetes, preexisting cerebrovascular problems, and use of antiepileptic agents. However, it is well known that patients with SCLC often have impaired cognitive functioning compared with healthy controls, independently of the use of chemotherapy or radiotherapy. Moreover, brain metastases by themselves have an important negative effect on cognition and QOL. Another point to consider is that brain metastases in SCLC—unlike those in non-SCLC—are often multiple, with limited options for high-dose stereotactic radiosurgery (SRS). Furthermore, the risk of brain metastases near the hippocampus also is low in SCLC.[7] The use of modern radiotherapy techniques that reduce doses to the hippocampus,[7] as well as the use of anti-Alzheimer drugs such as memantine and donepezil,[8] may reduce the cognitive effects of PCI—although the effectiveness and safety of these approaches remain to be evaluated in prospective clinical trials.

Second, some have questioned whether PCI would continue to show a beneficial effect if brain magnetic resonance imaging (MRI) were repeated after completion of chemotherapy. Repeat MRI could detect subclinical brain metastases; exclusion of these patients might, at least theoretically, reduce the absolute and relative effect of PCI on the incidence of brain metastases. From a clinical viewpoint, the finding of subclinical brain metastases on MRI is less relevant because in general, whole-brain radiation therapy (WBRT) and PCI use similar dose-fraction schemes (25-30 Gy in 10 fractions).

The discussion regarding MRI was intensified after the presentation of a Japanese study on ES-SCLC patients in 2014.[9] In that study, brain MRI was performed after chemotherapy and at regular intervals during follow-up. The study, which was designed as a superiority study with OS as the primary endpoint, closed early owing to futility. The likelihood of detecting a survival benefit in the PCI arm was less than 0.1%. The discussion about the role of PCI in ES-SCLC was fueled and biased by the incorrect and misleading title, which used the words "detrimental effect on the overall survival." There are a few additional caveats to take into consideration. The Japanese study accrued slowly, and in 4 years only 160 patients were enrolled from 40 centers. This could suggest that patient selection played a role in the results. In addition, approximately two-thirds of patients in the control arm developed symptomatic or asymptomatic brain metastases, and approximately 80% were treated with radiotherapy. Brain MRI after chemotherapy generally is performed in LS-SCLC, but not in ES-SCLC. Additional brain MRI every 3 months during follow-up leads to a significant increase in costs, and about half of the patients will still need brain radiotherapy. The publication of this analysis is still awaited with interest.

> PCI should be withheld only if contraindications exist or the patient is at high risk for neurocognitive deterioration.

We have reanalyzed the effect of PCI on brain metastases and survival in the previous EORTC study of PCI. We excluded patients who either died or developed brain metastases in the first 8 weeks after randomization because such patients may have had subclinical brain metastases that would have been visible had MRI been performed. Even after the exclusion of these patients with early progression, we found a significant effect of PCI on brain metastases and OS. These data, which I presented at the 2015 World Congress on Lung Cancer in September, have not yet been published.

Conclusion

Should all patients with SCLC receive PCI if they have responded to treatment? Exceptions exist, but in general the answer should be yes. Based on the available evidence from the literature, PCI should be offered to all patients who have responded to treatment and should be withheld only if contraindications exist or the patient is at high risk for neurocognitive deterioration. The pros and cons of PCI should be individually weighted and discussed with the patient. Modern radiotherapy techniques may help to reduce the risk of side effects from PCI.

References

1. Aupérin A, Arriagada R, Pignon JP, et al; Prophylactic Cranial Irradiation Overview Collaborative Group. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med*. 1999;341(7):476-484.

2. Le Péchoux C, Dunant A, Senan S, et al; Prophylactic Cranial Irradiation (PCI) Collaborative Group. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol*. 2009;10(5):467-474.

3. Slotman B, Faivre-Finn C, Kramer G, et al; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672.

4. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. *J Clin Oncol*. 2009;27(1):78-84.

5. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015;385(9962):36-42.

6. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys*. 2013;86(4):656-664.

7. Kundapur V, Ellchuk T, Ahmed S, Gondi V. Risk of hippocampal metastases in small cell lung cancer patients at presentation and after cranial irradiation: a safety profile study for hippocampal sparing during prophylactic or therapeutic cranial irradiation. *Int J Radiat Oncol Biol Phys*. 2015;91(4):781-786.

8. Day J, Zienius K, Gehring K, et al. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. *Cochrane Database Syst Rev*. 2014;12:CD011335.

9. Seto T, Takahashi T, Yamanaka T, et al. Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): results of a Japanese randomized phase III trial [ASCO abstract 7503]. *J Clin Oncol*. 2014;32(3)(suppl).

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disease. OS benefits for patients with ES-SCLC are less clear. Aupérin and colleagues included approximately 15% patients with ES-SCLC, for whom OS gains and reduction in CNS relapse were similar to those seen for the entire population.[3] Slotman and colleagues reported a reduction in CNS relapse and improvement in OS at 1 year, whereas a trial by Seto and colleagues that was presented at the American Society of Clinical Oncology 2014 annual meeting was closed because of poorer survival in the PCI arm.[5,6]

Since the trials summarized by Aupérin and colleagues and Meert and colleagues, there have been significant changes in staging and response evaluation, the attention paid to modest but real changes in cognition and QOL, and management of evident brain metastases. We address each of these in considering whether the risk-benefit ratio of PCI remains as favorable as presumed.

Stage Migration

The meta-analyses published by Aupérin and colleagues and Meert and colleagues required no evidence of brain metastases at enrollment; metastases were determined only by head computed tomography or absence of symptoms.[3] Seute and coinvestigators also noted an increase in detected brain metastases, from 10% with computed tomography to 24% with MRI.[7] Manapov and colleagues reported brain metastases in 13 of 40 patients with LS-SCLC who were in complete remission after initial chemoradiotherapy when these patients were imaged with MRI prior to PCI.[8] Restaging with MRI immediately before PCI will reduce the number of candidates for PCI but may increase its efficacy via lower tumor burden in patients receiving PCI.

Toxicity

Increased toxicity of PCI given at a high dose per fraction or concurrently with chemotherapy is a well-documented phenomenon. Even alone, however, PCI can have detrimental neurocognitive effects. Wolfson and colleagues reported that 60% of patients receiving PCI experienced neurocognitive decline (1 standard error decrease in at least 1 of 4 neuropsychological scales) at 1 year.[2] Gondi and colleagues described declines in verbal memory and QOL scales following PCI.[9] WBRT doses used in treating overt brain metastases are only modestly greater than those typically used in PCI (30 Gy in 10 fractions vs 25 Gy in 10 fractions) and are known to produce progressive cognitive impairment.[10] Trials by NRG Oncology exploring PCI with hippocampal avoidance and/or neuroprotective agents such as memantine are attempts to reduce neurotoxicity from PCI while retaining its effectiveness.[11]

Treatment of Brain Metastases

Although management of intrathoracic LS-SCLC has not improved drastically in recent decades, detection and treatment of brain metastases has, in part based on the use of SRS. One retrospective study of 41 patients treated with up-front SRS for brain metastases from SCLC reported local control rates of 100% and 86% at 6 and 12 months, respectively.[12] Another review of 44 patients with brain metastases from SCLC examined the use of SRS alone or in conjunction with WBRT. OS was 14 months in those who received both vs 12 months in those who received SRS alone. Local control rates for all patients were 90% at 6 months and 86% at 12 months. However, 61% of patients acquired new brain metastases outside the treated area, arguing for inclusion of WBRT at time of recurrence.[13]

> It is time to reassess the blanket recommendation of PCI for all patients with SCLC responding to initial therapy.

A New Role for PCI

Ozawa and colleagues reported a single-institution retrospective analysis of a policy in which patients who had LS-SCLC with a complete or good partial response and negative MRI after induction therapy were followed without PCI, and emergent brain metastases were treated with SRS when feasible.[14] They were compared with a concurrent but nonrandomized group of patients who received PCI. For patients with stage III disease, neither incidence of brain metastases nor OS differed between the 2 groups.

With considerable variation in primary treatment and a small sample size, their conclusion that limiting PCI may be feasible clearly requires further investigation.

A prospective trial is warranted to evaluate this alternative to universal PCI. Patients with LS-SCLC would be enrolled at diagnosis and staged with positron emission tomography and MRI. They would then undergo a standard regimen of chemoradiation followed by prompt restaging, including brain MRI, stratification by baseline neurocognitive function, and randomization. The experimental arm would receive close follow-up with MRI every 3 months for 2 years, by which time most relapses usually occur. Patients developing brain metastases would be treated with SRS with or without WBRT based on the number and size of brain metastases. Neurocognitive and QOL assessments would be done every 3 months for 3 years. The control arm would receive PCI in addition to the management described for the experimental arm. Endpoints would include survival, control of disease in the brain, relapse-free survival, neurocognitive functioning, and QOL. We hypothesize that there may be little difference in OS between these regimens, but that neurocognitive function may be better for those who have avoided PCI.

In pediatric ALL, PCI works but is now limited to high-risk patients because of the development of equally effective and less toxic therapies. Although it is not time to draw the curtain on PCI in SCLC, it is time to reassess its role. PCI has a significant effect (50% relative reduction) on brain metastases but only small gains (5%) in long-term survival.[15] In part, we must decide whether it is better to cure a small subset of patients at the cost of widespread exposure to PCI or to palliate the majority of patients who succumb to extracranial disease despite PCI.

Conclusion

As William Blake wrote in *The Marriage of Heaven and Hell,* "The man who never alters his opinion is like standing water, and breeds reptiles of the mind." With improved evaluation of response and CNS imaging, better treatment of overt brain metastases, and greater attention to neurotoxicity, it is time to reassess the blanket recommendation of PCI for all patients with SCLC responding to initial therapy.

Now that personalized cancer therapies are emerging, the decision to implement or withhold PCI may be based on combined analysis of primary tumor response, meticulous reimaging of the CNS, molecular profiling of the primary tumor, and assessment of the patient's baseline neurocognitive function rather than a one-size-fits-all strategy.

References

1. Zhang W, Jiang W, Luan L, Wang L, Zheng X, Wang G. Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*. 2014;14:793.

2. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(1):77-84.

3. Aupérin A, Arriagada R, Pignon JP, et al; Prophylactic Cranial Irradiation Overview Collaborative Group. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med*. 1999;341(7):476-484.

4. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*. 2001;1:5.

5. Slotman B, Faivre-Finn C, Kramer G, et al; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672.

6. Seto T, Takahashi T, Yamanaka T, et al. Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): results of a Japanese randomized phase III trial [ASCO abstract 7503]. *J Clin Oncol.* 2014;32(3)(suppl).

7. Seute T, Leffers P, ten Velde GPM, Twijnstra A. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). *Cancer*. 2008;112(8):1827-1834.

8. Manapov F, Klautke G, Fietkau R. Prevalence of brain metastases immediately before prophylactic cranial irradiation in limited disease small cell lung cancer patients with complete remission to chemoradiotherapy: a single institution experience. *J Thorac Oncol*. 2008;3(6):652-655.

9. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys*. 2013;86(4):656-664.

10. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): a phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases [ASCO abstract LBA4]. *J Clin Oncol.* 2015;33(15)(suppl).

11. Snider JW III, Gondi V, Brown PD, Tome W, Mehta MP. Prophylactic cranial irradiation: recent outcomes and innovations. *CNS Oncol*. 2014;3(3):219-230.

12. Yomo S, Hayashi M. Upfront stereotactic radiosurgery in patients with brain metastases from small cell lung cancer: retrospective analysis of 41 patients. *Radiat Oncol*. 2014;9:152.

13. Wegner RE, Olson AC, Kondziolka D, Niranjan A, Lundsford LD, Flickinger JC. Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(3):e21-e27.

14. Ozawa Y, Omae M, Fujii M, et al. Management of brain metastasis with magnetic resonance imaging and stereotactic irradiation attenuated benefits of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. *BMC Cancer*. 2015;15(1):589.

15. Arriagada R, Le Chevalier T, Rivière A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. *Ann Oncol*. 2002;13(5):748-754.