Models Support Prophylactic Cranial Irradiation

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In this issue of the *Journal of Clinical Oncology*, Lee et al.

1 present a rather unique and useful statistical interpretation of the waxing question of prophylactic cranial irradiation (PCI) for patients with small-cell lung cancer (SCLC). The concept of PCI for SCLC has its origins in the comparison of the behavior of this disease with childhood leukemia, a disease that is essentially systemic in nature, widespread at diagnosis, and exquisitely chemosensitive, with a high rate of complete response. Unfortunately, SCLC is also characterized by frequent relapse, with the CNS—especially the brain—acting as a sanctuary site that frequently is involved at relapse. In most clinical observations, we suggest an approximate 50% risk of developing intracranial metastases within 2 years in the absence of PCI.

2 The widely accepted explanation for this observation is the presence of preexisting micrometastatic disease in the brain, which effectively remains unperturbed by systemic cytotoxic agents, the majority of which do not penetrate an intact blood-brain barrier (BBB) in sufficient quantities.

Just as the disease is exquisitely sensitive to chemotherapy, it is similarly responsive to radiotherapy, which is not impeded by the BBB. Therefore, in this context, the use of cranial irradiation to eradicate residual microscopic disease is intuitively logical, although the concept of prophylaxis associated with this is actually a misnomer.

3 A more detailed analysis of this subject raises several important issues: First, PCI is not harmless. Based on the total dose and fractionation as well as the sequencing with chemotherapy, serious neurocognitive decline has been reported in some patients receiving PCI. Second, PCI is not universally effective in preventing clinical relapse. There might be a dose-response relationship, but this has not been identified clearly, and high doses are associated with greater neurocognitive decline. Third, many patients experience treatment failure both intra- and extracranially at about the same time, and intracranial disease control therefore does not have a significant impact on survival. In such patients, there might be a clinical neurologic benefit from avoiding the overt manifestation of metastatic disease in the brain, but this has not been studied adequately.

As a consequence of these issues, the use of PCI traditionally has been restricted to patients with SCLC who have obtained a complete response to therapy. The expectation is that those patients who have not achieved a complete response to therapy are destined to experience treatment failure extracranially, and should not be exposed to PCI. In addition, the sequencing of PCI after completion of systemic therapy would likely result in lower neurotoxicity. The exact dose and schedule for PCI still remains a matter of great debate, but relatively short schedules, employing low doses per fraction and also low total doses are common; one example is the use of 25 Gy in 10 fractions of 2.5 Gy each.

Several clinical trials of PCI have demonstrated clearly a dramatic decrease in the development of brain metastasis in patients receiving PCI, and meta-analysis of the data demonstrate that control of intracranial disease actually results in a modest but real survival gain, the magnitude of which is comparable to that achieved with thoracic irradiation in SCLC. This survival benefit is not unexpected, given that the survival of patients who develop brain metastases is only about 3 months, and hence any retardation of this process should lengthen survival.

Despite these data, many patients with SCLC do not receive PCI, primarily for issues related to concerns about neurotoxicity. It is in this context that the manuscript by Lee et al.

4 provides an interesting decision analysis tool. Their model varies survival rates and the rate of PCI-associated neurotoxicity in SCLC, and allows one to compute quality-adjusted life expectancy (QALE) based on these two variables. Clearly, such a tool permits a clinician to estimate these two outcomes for their patients to project an expected QALE, allowing more informed decision making.

To illustrate the potential use of such a model, currently published survival data are a good starting point. The authors use 5-year survival rates of 26% and 22%, with and without PCI, respectively. Using these assumptions, an appropriate presumed risk level for PCI-associated neurotoxicity can now be assessed. The authors use two broad levels of neurotoxicity, low and moderate. As expected, when the rate of neurotoxicity is low, PCI clearly offers superior QALE, even when the degree of neurotoxicity is varied from mild to severe (QALEs of 4.31 v 3.7 and 4.1 v 3.7). Therefore, for a low rate of toxicity, the degree of toxicity does not overwhelm the QALE benefit. Even with a moderate incidence of neurotoxicity, PCI continues to offer superior QALE. Thus, current survival expectations would predict superior QALE for most scenarios for SCLC patients in complete response treated with PCI.

What if survival were to improve considerably? For example, in a recent small randomized trial from China, 5-year survival for PCI-treated patients was 35% compared with 24% for the non-PCI group, and the 2-year incidence of brain metastases was 3.8% v 32%, respectively. This would clearly put more patients at risk for delayed PCI-associated neurotoxicity, thereby reducing the benefit of intracranial disease control. The authors have modeled this scenario as well. For example, if the survival in the PCI treated patients reaches 40%, PCI continues to provide better QALE than no PCI for mild neurotoxicity, but not for substantial degrees of...
neurotoxicity (QALEs of 5.47 v 5.72). In fact, the modeling demonstrates the superiority of PCI over no PCI universally and independently under three conditions: a low rate of neurotoxicity, a mild degree of neurotoxicity, and a shorter survival. However, as 5-year survival improves beyond 40%, the risk-benefit ratio for PCI will begin to diminish, and attention will have to be directed to reducing the neurotoxicity from PCI.

Simple radiation dose escalation to the whole brain is unlikely to improve intracranial control to a point where the QALE can be improved further. In a recent analysis based on a population registry, 1,417 new cases of SCLC treated in Saskatchewan, Canada, from 1981 to 1998, 244 were limited stage and treated with curative intent. The 10-year cause-specific survival rate was 15% ± 3%, and the data also showed that the absence of mediastinal lymphadenopathy and higher chest radiotherapy dose were significant prognostic factors for survival by multivariate analysis (P < .05). However, among the 163 patients administered PCI, a higher biologically effective dose to the brain did not improve survival or decrease the incidence of brain metastases.9 Of course, the full potential of dose fractionation has not been exploited for PCI. This is one of the few diseases in which several small fractions of radiation delivered in a short period of time has made a difference in local thoracic control and overall survival. From these data, it might be logical to assume that smaller fractions would be equally effective in controlling microscopic disease in the brain, hypothetically resulting in lower neurocognitive decline, thereby improving the therapeutic ratio and changing the model described by the authors. Recently, we and others have started exploring the possibility of hippocampal-sparing whole-brain radiotherapy, which could also potentially alter the PCI therapeutic ratio.10

In this context, it is useful to note that some efforts have been made to use chemotherapy to treat SCLC brain metastases. In one recent report, topotecan was used in pretreated patients with SCLC who experienced relapse with symptomatic brain metastases. Cerebral metastases responded in 33% of patients and median time to progression was 3.1 months, with median survival of 3.6 months.11 Although this represents only modest activity, future studies potentially could evaluate agents such as topotecan and temozolomide, which penetrate the BBB, perhaps allowing a lowering of the PCI dose, and thereby further altering the therapeutic window.

What are the potential weaknesses of this model? The survival function is supported by rather robust data, but the calculation of neurocognitive toxicity is a best guess. As the authors point out, these patients have a high level of baseline neurocognitive deficits before any therapy, and most trials have not evaluated neurologic and neurocognitive function in these patients prospectively or formally. The authors elected to study two case scenarios in depth: 30% (low) and 50% (moderate) rates of neurotoxicity. These levels, of course, are arbitrary. As the authors point out, although older studies described up to a 50% rate of neurocognitive deficits, modern trials with less aggressive fractionation schedules have described much lower rates of neurotoxicity. Therefore, the use of this model for an individual patient is limited because there are no reliable methods to predict an individual patient’s neurologic outcome.

Second, the quality function in QALE requires an assumption that permits the conversion of neurotoxicity to a certain level of decline in quality of life, and this step is also a best-guess scenario, rather than data driven.

Third, we and others have shown that progressive intracranial disease leads to neurologic and neurocognitive decline and a concomitant reduction in quality of life with a reduced QALE.12 Patients with SCLC who do not receive PCI are obviously spared the neurotoxicity of PCI but are also exposed to the neurologic decline associated with progressive brain metastases, resulting in a lowering of their QALE, which has not been modeled in the article by Lee et al.1 However, despite these limitations of the model, at current rates of survival and observed neurotoxicity, PCI consistently results in superior QALE for patients with SCLC, and this conclusion should provide further support to continue its use in appropriately selected patients.

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REFERENCES
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The author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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