Running in Place: The 20th Anniversary of the NCCN Small Cell Lung Cancer Guidelines Panel

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Although I was not involved in the development of the original NCCN Guidelines for Small Cell Lung Cancer (SCLC) 20 years ago, I have now been a member of the panel for 16 years and have served as panel chair since 2006. Most importantly, I had saved a copy of the original guideline, torn neatly from the November 1996 issue of Oncology.¹

As part of the guideline development process, each panel meets annually to discuss recent studies relevant to the field and to determine how these findings might affect patient management. The goal of this exercise is to keep the guidelines as up-to-date as possible. Unfortunately, SCLC has developed a reputation for stagnation, with little change in our basic treatment strategies over the past 30 years. This lack of progress is epitomized by the continued use of platinum/etoposide regimens as standard first-line chemotherapy for patients with both limited- and extensive-stage disease. Frequently, our annual review of the SCLC literature seems like merely an exercise in running in place, with the only changes being improvements in formatting and punctuation. So, when I was asked by the NCCN office—as part of the NCCN’s 20th anniversary events—to provide a list of 3 “key treatment advances” in SCLC over the past 20 years, my first reaction was, “You’re kidding, right?”

Indeed, when I compared the original NCCN Guidelines for SCLC to the current one, our lack of substantial progress became depressingly apparent. The recommended treatment paradigms have remained virtually unchanged: surgery for stage I disease, cisplatin/etoposide plus concurrent thoracic radiation for limited-stage disease, combination chemotherapy for extensive-stage disease, and prophylactic cranial irradiation (PCI) for those with good response to initial therapy. Sure, there were some minor changes, such as no longer recommending cisplatin/etoposide alternating with CAV (cyclophosphamide/doxorubicin/vincristine) for extensive-stage disease, but the basic approaches had remained remarkably unchanged.

Yet, I had been asked to find key advances, and if there is one thing I do well, it is follow directions, so I looked deeper. Yes, we have made advances. Granted, calling them “key” might be a bit of a stretch, but we have clearly made some movement in the right direction. What has most clearly changed is the strengthening of recommendations based on the results of randomized trials and meta-analyses reporting significant survival benefits for particular interventions. For example, in 1996, both PCI and salvage chemotherapy were included as category 3 options (“Items that will require further analysis for firm recommendations”). Both are now category 1 recommendations (“Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate”), thanks to the diligent work of clinical investigators throughout the world.² ³ Even an approach we now consider routine, the use of concurrent chemoradiation for limited-stage disease, was deemed category 2 in 1996 (“Recommendations that are somewhat controversial”). It is now category 1 based on clinical trials showing a consistent survival advantage.⁴ ⁵

While these may seem like minor changes, the support of guideline recommendations by high-quality evidence is not a trivial matter. It is of utmost importance to our patients that we have confidence in the potential benefits of our interventions, particularly when they also carry substantial risk.

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Several other potential key advances remain controversial. Despite favorable results from a large randomized trial, the benefit of hyperfractionated thoracic radiation continues to be debated.\(^6\) Hopefully, well-designed, ongoing trials will provide a more definitive assessment of this strategy. Two years ago, PCI for patients with extensive-stage SCLC gained a category 1 recommendation based on the positive results of a randomized European study.\(^7\) However, conflicting data from Japan were recently presented.\(^8\) These data raised questions as to the true benefits of this approach, and resulted in its demotion to a category 2A recommendation (“Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate”), pending the final publication of the Japanese study.\(^9\)

Recently, a randomized study reported that thoracic radiation was associated with significant improvement in 2-year overall survival in patients with extensive-stage SCLC who showed response to first-line chemotherapy. This finding would seem to earn category 1 status, but at our recent panel meeting, this strategy was designated a category 2A recommendation, because 2-year survival was only a secondary end point. The primary end point of the study, 1-year survival, was not significantly improved.\(^5\)

On comparing the original and current guidelines, I also noted other substantial improvements beyond those within the treatment algorithms. The NCCN Guidelines Panel now has much broader representation from all the disciplines involved in caring for patients with SCLC. In 1996, the 8-member panel included 4 medical oncologists, 3 radiation oncologists, and 1 gynecologic oncologist (well, I did recently see a woman with a vulvar metastasis). Now, our panel has 28 members representing not only medical and radiation oncology, but also thoracic surgery, pathology, and diagnostic radiology.

Another substantial improvement in the NCCN Guidelines for SCLC (and many others) has been the inclusion of “Principles of” sections that provide relevant, detailed, clinical guidance on the use of surgery, radiation, chemotherapy, and supportive care; practical information that is difficult to find in standard textbooks or other online resources.

Also over the past 20 years, a shift has occurred in the concepts used to justify recommendations presented in the guidelines. When initially developed, the categories used to define the strength of recommendations were purely based on the consensus of the panel, without any mention of levels of evidence. Now, although the NCCN Guidelines remain somewhat consensus-based, all category definitions include consideration of the level of evidence. Purely evidence-based guidelines are not of much use to the practicing oncologist, since most of the clinical decisions we make on a daily basis have little, if any, available evidence to support one approach over another. Thus, this balance between expert judgment and evidence drives the high level of clinical utility that the NCCN Guidelines have achieved.

Thus far, despite the exponential growth in our understanding of SCLC biology over the past 20 years, the “precision oncology” revolution has seemingly passed by SCLC. But I see hints that our fortunes may be changing. Genomic analyses are now identifying more and more rational therapeutic targets\(^10,11\) and the number of clinical trials for patients with SCLC continues to grow. In addition, immunotherapy and strategies targeting stem cell pathways are beginning to show promise in early phase clinical trials. God willing, I will still be kicking around 20 years from now to witness the continued evolution of the NCCN Guidelines for SCLC and to see real progress against this dreadful disease.

References

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