Therapeutics Approaches in the Treatment of Limited Small-Cell Lung Cancer

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In recent years, of all malignancies, lung cancer is the leading cause of death in Korea. About 15~20 percent of lung cancers are small-cell lung cancer. A limited stage small-cell lung cancer, which clinically exists in one side of chest, comprises 30~40 percent of all small-cell lung cancer. Since the late 1960s, when chemotherapy was reported to increase survival, it has played an essential role, along with radiotherapy, in the treatment of limited disease (LD) small-cell lung cancer. At present, the surgical modality is being applied only to stage I cancers, with no mediastinal LN involvement. In 1992, two meta-analyses revealed that combination chemotherapy, combined with thoracic radiotherapy, proved a small, but significant, advantage in the survival (14% improvement in median survival) of LD patients, compared to chemotherapy alone. Since then, the combined modality of chemotherapy and thoracic radiotherapy became the standard treatment of LD small-cell lung cancer (1).

Instead of the CAV ( Cyclophosphamide, Adriamycin and Vincristine) regimen, which has been used as a standard treatment since the late 1970s, EP (Etoposide and Cisplatin), since 1992, has become a standard regimen in the majority of clinical trials in small cell lung cancer. The results released in 1992, by Roth et al., and by Sundstrom et al. in 2002, support this background (2,3). That is, EP combination chemotherapy has shown equal, or better, efficacy than CAV in phase III clinical trials. In addition, in terms of toxicity, EP showed less myelosuppression and more mucosa sparing effects when combined with radiation, which might reduce intra-thoracic complications, such as esophagitis and radiation pneumonitis. Therefore, with this relatively lower toxicity, EP could be administered without impairment of dosage, along with radiation, which could be a reason for the better outcomes in several EP-based clinical trials.

There have been several therapeutic approaches based on two modalities, including chemotherapy and radiotherapy, to improve outcomes in LD small-cell lung cancer.

The first issue concerned whether it would be better to administer radiotherapy concurrently, or sequentially, with chemotherapy, in terms of survival and toxicity. It would not be easy to find a nicely designed phase III clinical trial that directly compared the two modalities. Moreover, the meta-analyses released in 1992 did not show any difference between the two treatment modalities (1). However, these analyses were based on the CAV regimen, which was too toxic to administer concurrently with radiotherapy. As a matter of fact, since the era of EP based chemotherapy in LD small-cell lung cancer, while sequential chemoradiotherapy did not show any superiority to chemotherapy alone, concurrent chemoradiotherapy showed better survival. Therefore, concurrent chemoradiotherapy, based on the EP regimen, studied by Sohn et al in this issue of the journal, is regarded as the standard treatment in LD small-cell lung cancer (4).

The second issue was about the timing of radiotherapy. In 1993, a phase III study by Murray et al compared two concurrent chemoradiotherapies, starting on the second or sixth cycle of chemotherapy, which was based on a CAV/EP alternating regimen. This study reported a better survival in the early concurrent chemoradiation arm. They explained there would be three groups according to the distribution of chemosensitive and chemoresistant cell clones. The first group comprised of all chemosensitive cell clones, in both the intra-thoracic and systemic areas (5~10%). The chemosensitive cell clones in the second group were distributed systemically, but in the intra-thoracic area, where uncountable cells are cloning, there would be chemoresistant strains mixed with the chemosensitive ones (30~40%). The third group was composed of a mixture of chemosensitive and chemoresistant cells, in both the intra-thoracic and systemic areas (50~60%). The authors pointed out there would be great benefit in the case of the second group if the radiotherapy were administered earlier, before metastasis of the chemoresistant clones could occur. It is recommended that radiotherapy be started as soon as, and at least within the 6 weeks, of the commencement of chemotherapy under these theoretic background (6).

The third issue was regarding hyperfractionation. The small-cell lung cancer cells have a high growth fraction and short cell cycles. These are the theoretic bases why hyperfractionation radiotherapy needs to be testified whether it is more effective than once daily radiation. In 1999, a phase III clinical trial was reported by Turrisi et al, where survival between once and twice daily radiation (hyperfractionation) were compared in patients who were supposed to be given 4 cycles of EP chemotherapy. The total dose of radiation was equal in both arms (45 Gy). The hyperfractionation arm was better in terms of local relapse (36% vs. 52%, P=0.06) and median survival (23 mo. vs. 19 mo. P=0.04). One more point that needs to be checked again with this article is the outcomes of both arms. This trial has tracked down the concept already discussed, which is that of early concurrent chemoradiotherapy, based on the EP regimen. The two-year survival of the both two arms ranged between 41~47%, which was almost twice that of the previous trials that did not comply with the principles we have mentioned, and the toxicities were tolerable (7). Reviewing the report of Sohn et al in this journal, we could assume the reason
for the 24% two-year survival of this trial was as a result of only 33 of the 50 patients (66%) could be administered with radiotherapy.

The forth matter; at present, four to six cycles of chemotherapy are recommended as an optimal in LD small-cell lung cancer. Maintenance therapy is considered to be of no value, but there would be some role in selected patients, especially those who have achieved CR (8).

The fifth topic relates to prophylactic cranial irradiation (PCI). In 1999, Auperin et al. reported a meta-analysis regarding prophylactic cranial irradiation in patients having achieved complete remission of approximately 1000 small cell lung cancer patients (9). With the introduction of PCI, the three-year survival improved from 15 to 21% (P<0.01), and brain metastasis has been reduced, with statistical significance. Prophylactic cranial irradiation dosing of 24–30 Gy is being recommended to patients having achieved CR within 2 weeks of the completion of chemotherapy.

The last issue we need to consider relates to the struggle in the development of new chemotherapeutic drug. As the issue of this journal indicates, 89% of first relapse were distant metastases, which has lead to the demand for better combination chemotherapy to replace the EP regimen. In 2002, the Japanese researchers, Noda et al., reported a better survival with irinotecan and cisplatin, compared to EP, combination chemotherapy in extensive stage small cell lung cancer (median survival 12.8 mo. vs. 9.4 mo. P<0.002) (10). Currently, this regimen in LD small cell lung cancer, with the exception of one phase I clinical trial (11), is rarely reported. It would be desirable to continue clinical trials based on the knowledge we have learnt from all the previous and important clinical studies, using the attractive combination of irinotecan and cisplatin in LD small-cell lung cancer, in the future.

REFERENCES