



Superiority of Concomitant Chemoradiation Over Sequential Chemoradiation in Inoperable, Locally Advanced Non–Small Cell Lung Cancer: Challenges in the Selection of Appropriate Chemotherapy

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Treatment of inoperable, locally advanced non–small cell lung cancer (LA-NSCLC) is challenging and requires a multidisciplinary approach considering both local therapy and systemic therapy. Based on the results from several phase III studies and 2 meta-analyses, the use of concomitant chemoradiation therapy (ChRT) could significantly improve overall survival and is considered the standard of care in LA-NSCLC with good performance status. Currently, no evidence has shown a significant survival benefit of third-generation regimens applied in combination with ChRT compared with second-generation regimens. For regimens concomitant with radiation therapy, full-dose chemotherapy (such as cisplatin and etoposide or cisplatin and vinblastine) might be preferred. Additional full-dose consolidation paclitaxel-carboplatin is recommended when patients receive weekly paclitaxel-carboplatin ChRT. Effective novel chemotherapy agents or targeted therapies are required to further improve the outcome of patients with LA-NSCLC. In addition, personalized medicine concomitant with radiation therapy is a promising approach. However, little evidence exists concerning the effectiveness of this novel approach.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide. More than 85% of these patients belong to the non–small cell lung cancer (NSCLC) histopathologic subtype. Up to one-third of these patients present with locally advanced NSCLC disease (LA-NSCLC) that is surgically unresectable,^{1,2} for which concurrent chemotherapy and radiation therapy (RT) offer the best potential for cure.³ Although pivotal trials

have shown a significant improvement in survival for this bimodality therapy,⁴ treatment of LA-NSCLC remains challenging, with a survival rate of less than 20% at 5 years. The latter finding might be primarily owing to the significant heterogeneity within LA-NSCLC and the requirement of the treatment modalities to simultaneously control local, regional, and distant metastatic disease. In addition, concomitant chemoradiation therapy (ChRT) has demonstrated increased toxicities.

Presently, many questions remain unanswered concerning combining RT and chemotherapy, including those related to selecting appropriate agents based on stage and histology, delivering treatment concomitantly with RT rather than sequentially, and evaluating potential gains with novel agents. Furthermore, in most trials, the selection criteria have focused on patients with a good performance status (PS), and limited data are available among those with a less-favorable profile (eg, elderly patients). Recent developments regarding each of these areas are reviewed here.

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ChRT Is the Standard Care for LA-NSCLC

Rationale for Combining RT and Chemotherapy

The biological rationale underlying the combination of RT and chemotherapy has been investigated. Theoretically, spatial cooperation and enhancement of tumor response are considered 2 important ways to improve the therapeutic effect in NSCLC.⁵ In terms of spatial cooperation, the predominant effect of RT is at the primary tumor site or locoregional disease, whereas chemotherapy is intended to act systemically on the micrometastatic spread of tumor cells. Regarding tumor response enhancement, chemotherapeutic agents could add to or modify the DNA damage caused by RT and ultimately lead to enhanced effects on the tumor.⁶ For example, cisplatin- and etoposide-based concomitant chemotherapy can induce both radiation-induced single-strand and double-strand DNA breaks, resulting in enhanced efficacy together with the administration of RT. Another example is fluoropyrimidines, which can synchronize tumor cell populations in the radio-sensitive G2-M phase, thus enhancing responses to RT. Clinically, the empirical rationale for combining RT and chemotherapy is the all-too-frequent failure of either modality when administered alone. RT alone often fails to treat distant subclinical metastases. Chemotherapy alone often fails to eradicate bulky, unresectable tumors and is unlikely to adequately treat NSCLC. As pivotal trials have shown, combined chemotherapy and RT could improve not only local tumor control but also overall survival (OS).⁷⁻¹⁵

Survival Benefits of ChRT

The superiority of ChRT over sequential therapy in patients with LA-NSCLC has been supported by multiple trials.⁴ Table 1 lists several large prospective phase III studies published over the past 2 decades.⁸⁻¹⁵ In summary, the arm-specific median survival ranged from 13.4-18.7 months for the concomitant group and from 11-14.6 months for the sequential group. This survival benefit with ChRT was further confirmed by 2 meta-analyses published in 2010. In an updated Cochrane meta-analysis, 6 trials that included 1024 patients who received concomitant vs sequential ChRT were analyzed.¹⁶ A significant benefit in OS was shown (hazard ratio [HR] = 0.74; 95% CI: 0.62-0.89; 702 participants) and a 10% absolute OS benefit at 2 years. A second meta-analysis was performed using individual patient data from 1205 patients enrolled in 6 randomized phase II-III trials.⁴ Similarly, this meta-analysis demonstrated that, compared with sequential treatment, ChRT conferred a significantly higher rate of OS (HR = 0.84; 95% CI: 0.74-0.95; $P = 0.004$) with an increase of 5.7% at 3 years (from 18.1%-23.8%) and an increase of 4.5% at 5 years (from 10.6%-15.1%). Regarding locoregional progression analysis, which was based on 5 trials and 1092 patients, ChRT also resulted in a significantly lower rate (HR = 0.77; 95% CI: 0.62-0.95; $P = 0.01$) with an absolute decrease of 6.0% at 3 years (from 34.1%-28.1%) and an absolute

decrease of 6.1% at 5 years (from 35.0%-28.9%). However, there was no difference between the 2 treatments concerning distant progression (HR = 1.04; 95% CI: 0.86-1.25; $P = 0.69$). Thus, the survival benefit of ChRT is predominantly related to improvement in local control, leading to an OS improvement.

Toxicities Associated With ChRT and Patient Selection

Compared with sequential chemotherapy followed by RT, ChRT is supposed to be associated with higher rates of treatment-related morbidity, such as severe esophagitis, pneumonitis, and hematologic toxicities. However, based on the individual patient data from the meta-analysis of Auperin et al,⁴ only a significantly higher relative risk of acute grade 3-4 esophageal toxicity (from 4%-18%; $P < 0.001$) was observed. There was no difference in acute grade 3-4 pulmonary toxicity ($P = 0.13$), and it was impossible to pool the severe hematologic toxicity data because the rates were highly variable across trials, ranging from 20%-90%. Another systematic review also compared treatment-related morbidity and mortality for concomitant vs sequential ChRT.¹⁶ Again, there were only higher rates of grade 3 or higher esophagitis in the concomitant group (relative risk = 4.96; 95% CI: 2.17-11.37). No significant differences in hematologic toxicity and treatment-related mortality were found between the 2 groups.

Over recent years, the overall compliance with ChRT in clinical practice has been remarkably improved with adequate supportive measures. As demonstrated by multiple clinical trials, factors correlating with the increased use of ChRT for LA-NSCLC include lower age, good PS, weight loss less than 5%, and lack of comorbidities.

Chemotherapy Optimization in LA-NSCLC Treated With ChRT

Although ChRT has been established as the standard treatment for LA-NSCLC, the high rate of failure and low rate of patients' long-term survival are still disappointing.⁸⁻¹⁵ Thus, improvement in treatment strategies is warranted, such as optimization of current chemotherapy regimens, use of novel chemotherapy agents, and combination with targeted therapy. The current ChRT protocols include 3 categories: first, RT with full-dose, old-generation chemotherapy combinations such as cisplatin-etoposide (EP), cisplatin-vindesine-mitomycin (MVP), and cisplatin-vinorelbine (NP) regimens; second, RT with reduced-dose, new-generation chemotherapy combinations such as the paclitaxel-carboplatin (PC) regimen; and third, RT with daily or weekly low-dose chemotherapy such as low-dose cisplatin or carboplatin. Unfortunately, to date, there have been few published phase III studies to directly compare different chemotherapy regimens with concurrent RT and to establish a standard chemoradiation protocol for LA-NSCLC. However, it is widely believed that the combination of gemcitabine and RT would result in excessive pulmonary toxicity and should not be used for LA-NSCLC.^{17,18}

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