Concurrent Chemoradiation in Inoperable, Locally Advanced Non-small Cell Lung Cancer—Comparison of Efficacy and Toxicity in the Elderly

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Abstract

Clinicians are faced with the challenge of treating increasing numbers of elderly patients with locally advanced non-small cell lung cancer (LA-NSCLC) and comorbid conditions. In the younger patient, the benefit of combined chemoradiation using the concurrent modality compared with the sequential administration of both modalities has been established in several randomised trials and recent meta-analyses. Because of the underrepresentation of elderly patients in clinical trials on concurrent chemoradiation (CCRT) in LA-NSCLC, treatment guidelines for this age group are not well established. The objective of this article is to summarise the data on efficacy and toxicity of CCRT in the elderly.

Keywords

Locally advanced non-small cell lung cancer, concurrent chemoradiation, elderly, efficacy, toxicity

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The incidence of lung cancer diagnosed in the elderly population is rising as a result of increasing life expectancy. Patients aged over 65 years at diagnosis represent half of the population newly diagnosed with non-small cell lung cancer (NSCLC), while 30–40 % of cases are diagnosed in patients older than 70 years.[1] As reported by Balducci, the cut-off point at which an adult is considered 'elderly' has not been well defined, but commonly 70 years is considered to be the reference point in clinical trials. The age-related physiological changes that increase the risk of toxicity related to systemic therapy occur around 70 years of age.[2]

Extermann et al. have defined the geriatric oncology group of patients as "when the health status of a patient population begins to interfere with oncological decision-making guidelines".[3] Within clinical trials, this is defined by exclusion criteria and, as pointed out in the review by Pallis et al., a number of barriers (other than comorbid conditions) to the recruitment of older patients to cancer clinical trials have been revealed,[4] such as difficulty in accessing university hospitals, lack of adequate information about the availability of clinical trials, and perception of the individual physician that the patient would not be able to tolerate treatment. The conclusion of a prospective, population-based trial by De Ruysscher et al. on eligibility for concurrent chemoradiation (CCRT) concluded that more than half of patients with LA-NSCLC were theoretically not eligible because they had one or more important comorbid conditions or were 75 years or older.[5]

Consequently, prospective elderly-specific trials are lacking and treatment recommendations are made on the basis of retrospective data. These might suffer from selection bias, since elderly patients who meet protocol eligibility criteria often do not present with comorbid conditions or organ function failures that present in the real-life situation. Because of the rising incidence of NSCLC in the elderly population, biological age rather than chronological age should guide clinicians in deciding on treatment strategy. Geriatric scoring systems can be implemented in an attempt to better define the role of comorbid disease in the elderly population. In addition, technological advances in the field of radiotherapy could contribute to increased efficacy[6] and reduced side effects[7] of treatment in the LA-NSCLC patient population.

Available Evidence Supporting Concurrent Chemoradiation in the Elderly Population

Regarding the use of radiotherapy in elderly patients, it has been reported that elderly patients are not at risk of increased acute or late toxicity after radiotherapy with curative doses.[8,9] The addition of chemotherapy to radiation has an additional effect on survival in LA-NSCLC at the price of increased toxicity.[10] Concurrent chemoradiation (CCRT) has a temporary impact on quality of life, primarily because of fatigue and esophagitis during and shortly after treatment. However, the quality of life usually recovers to baseline values within three months.[11] The recent meta-analysis of concurrent versus sequential chemoradiation by Aupérin et al.[12] demonstrated the improved overall survival of the concurrent approach, with an absolute benefit of 5.7 % at three years and 4.5 % at five years, as compared with sequential chemoradiation, primarily because of a better locoregional control. The effect of CCRT on distant progression was not different from that of the sequential approach. Acute

Table 1: Retrospective Subgroup Analyses of Chemoradiation Trials for Non-small Cell Lung Cancer Comparing Treatment Outcomes between Elderly and Younger Patients

Study	Trials	No. of Patients	Efficacy	Toxicity	MST
Langer et al., 2002[18]	Phase III trial: CCRT (qd or bid) versus SCRT	<70 y: 491 ≥70 y: 104	In favor of CCRT for >70 y	Short-term toxicities (G >3 neutropenia and esophagitis) more pronounced in elderly, long-term toxicities similar	≥70 y: 10.8 months (SCRT) versus 16.4 months (CCRT bid) versus 22.4 months (CCRT qd)
Schild et al., 2003[19]	Phase III trial: CCRT bid versus CCRT qd	<70 y: 181 ≥70 y: 63	Survival not age-related	More myelosuppression and pneumonitis in elderly	<70 y: 5-y survival rate 18 % ≥70 y: 5-y survival rate 13 %
Rocha Lima et al., 2002[14]	Two CALGB Phase III trials: SCRT versus CCRT	<70 y: 222 ≥70 y: 31	Survival not age-related	More hematologic toxicity in elderly	<70 y: 11–15 months ≥70 y: 13 months
Werner-Wasik et al., 2000[16]	Nine Phase I–III trials: RT, SCRT, or CCRT	<70 y: 1,565 ≥70 y: 429	Survival age-related	NR	<70 y: 10–16 months ≥70 y: 3–6 months
Movsas et al., 1999[17]	Six Phase II and III trials: RT, SCRT, or CCRT	<70 y: 835 ≥70 y: 144	<70 y: improved survival with CMT >70 y: best quality-adjusted survival with RT alone	NR	<70 y: 12–14 months ≥70 y: 11 months

bid = twice a day; CALGB = Cancer and Leukemia Group B; CCRT = concurrent chemoradiation; CMT = combined modality treatment; G = grade; MST = median survival time; NR = not reported; qd = daily; RT = radiotherapy; SCRT = sequential chemoradiation; y = years.
Source: modified from Gridelli et al., 2007.[27]

grade 3–4 esophageal toxicity was increased from 4 % to 18 % but was manageable. Since CCRT leads to significantly higher side effects, it is often reserved to younger patients with few comorbid conditions.[4,13] This underrepresentation of elderly patients in clinical trials restricts the available clinical trial data to guide physicians in treatment decisions for elderly patients. Controlled clinical trials especially designed toward the elderly, including geriatric evaluations, are indicated.[14]

Only one prospective elderly-specific Phase III trial has evaluated CCRT versus radiotherapy (RT) alone.[15] Patients were randomly assigned to RT alone (60 Gy) or to CCRT (same RT with concurrent administration of carboplatin 30 mg/m^2). The trial was prematurely closed for accrual after the occurrence of four treatment-related deaths, of which three occurred in the CCRT arm. For the 46 patients treated at that time, the median survival time was not significantly different between both arms (14.3 months with RT alone compared with 18.5 months in the CCRT arm). Because of the small number of patients included and protocol violations concerning the radiation field that might have influenced half of the treatment-related deaths attributed to pneumonitis, the investigators concluded that the efficacy of concurrent carboplatin plus radiotherapy in elderly patients remains unclear and no definitive conclusions can be drawn from this trial.

When looking at retrospective subgroup analyses of randomised chemoradiation trials comparing treatment outcomes between elderly and younger patients, results are inconsistent (see *Table 1*). The secondary analysis of a Radiation Therapy Oncology Group (RTOG) study demonstrated inferior outcomes of chemoradiation in the elderly and those with poorer performance status.[16] Movsas et al. reported that the best quality-adjusted survival in older patients was achieved with RT alone.[17] In contrast, subset analyses of several other trials[14,18–20] and the NSCLC Collaborative Group meta-analysis[21] concluded that the survival advantage of chemoradiation was not related to age.

Valuable information can be obtained from population-based studies that examined the effects of combined modality treatment in the elderly population. These are treatment results obtained in the heterogeneous population of older patients with comorbid conditions and poorer performance status (PS) who are not treated in a clinical trial setting. Davidoff and colleagues[22] investigated the effects of combined modality treatment in elderly LA-NSCLC patients using Surveillance, Epidemiology and End Results–Medicare data and concluded that survival benefits associated with combined modality treatment in clinical trials can be extended to the elderly population in routine daily practice. The absolute survival duration observed is shorter than that reported in clinical trials, reflecting the higher comorbid conditions or poorer PS of the elderly patients treated outside the clinical trial setting.

Concurrent Chemoradiation in the Frail Elderly

We could only identify one institutional report, by Semrau et al., on CCRT in elderly LA-NSCLC patients presenting with multiple morbidities.[23] The authors reported on their six-year experience of CCRT with vinorelbine plus a platinum compound. The frail elderly population was defined as patients with an increased risk profile of treatment side effects due to World Health Organization (WHO) performance status 2–3, cardiac, renal or pulmonary failure, extensive weight loss before treatment, or age 71–78 years. A total of 66 patients received CCRT, with manageable toxicity. The dose intensity of chemotherapy and radiotherapy was 62 % and 94 %, respectively. In this population with poor prognostic factors, dose-adjusted chemotherapy and radiotherapy was feasible, and the survival rates of 25 % at two years and 8 % at five years were comparable to those achieved in other studies.[23]

Technological Advances in the Field of Radiotherapy

Technological advances in radiotherapy treatment planning and delivery have occurred in the past five years, including incorporation

of functional imaging by [18F]deoxyglucose-positron emission tomography scan in the planning process,[5] three-dimensional conformal radiotherapy, four-dimensional computed tomography,[7] respiratory gating, intensity-modulated radiotherapy, helical tomotherapy, and image-guided radiotherapy. These newer radiation techniques significantly reduce toxicity by limiting the volume of irradiated lung tissue.[7]

Irrespective of age, the acute and late toxicity profile after high-dose radiotherapy is related to the extent of the radiation field. Only in the most recent studies on combined modality treatment has conformal radiotherapy been introduced. Most studies used two-dimensional large radiation fields that included elective nodal areas. Systematic integration of three-dimensional conformal radiotherapy and target delineation based on functional imaging will undoubtedly influence the esophageal and pulmonary toxicity after chemoradiation.

Our group has engaged in a Phase I/II radiation dose escalation trial using helical tomotherapy with a fixed low-dose of weekly chemotherapy consisting of cisplatin and docetaxel at a dose of 20 mg/m^2 each. The toxicity profile of this approach has been published earlier.[24] We thereafter compared treatment-related toxicity, impact of treatment on quality of life, and differences in outcome between younger (<70 years, n=42) and older (≥70 years, n=17) patients. Besides an increased rate of neutropenia, elderly patients did not experience increased toxicity or decreased quality of life after concurrent chemoradiation. A comparable survival was achieved, with a median survival time of 18.5 months in the younger versus 17.9 months in the older patient group (p=0.6105).

Comprehensive Geriatric Assessment-based Approach

The current standard of functional status assessment using Eastern Cooperative Oncology Group or Karnofsky scales poorly predicts functional impairment in the elderly.[25] A comprehensive geriatric assessment (CGA) is a multidisciplinary evaluation, by oncologists and geriatricians, in which the multiple problems of older patients are uncovered, described, and explained. It typically consists of evaluation of an older individual's functional status, comorbid conditions, cognition, psychological state, social support, and nutritional status and a review of the patient's medications.[26] There is strong evidence that a CGA detects problems that may have been missed by a regular clinical evaluation. Accumulating data show the benefit of incorporating a CGA in the initial evaluation of older patients with cancer, because it uncovers problems relevant to cancer care that would otherwise go unrecognized and can predict morbidity and mortality in older patients with cancer. Pre-treatment values of instrumental activities of daily living correlate with survival.[3] Therefore, the integration of geriatric assessment into studies with a high proportion of older patients needs to be encouraged.

Conclusions

Concurrent chemoradiation should be offered to elderly patients suffering from LA-NSCLC, since a survival benefit can be achieved. Even in the absence of prospective elderly-specific data, we encourage treatment of older patients with CCRT since elderly patients treated with CCRT outside the clinical trial setting experience the same survival benefit—albeit with a shorter survival duration. Elderly-specific CCRT trials incorporating modern radiation techniques and geriatric assessment should be encouraged to truly establish the place of CCRT in the older patient with LA-NSCLC. ■

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