Chemo-radiotherapy in lung cancer: state of the art with focus on the elderly population

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Introduction

Worldwide, lung cancer is the leading cause of cancer death in men and has surpassed breast cancer as the leading cause of cancer death in women in the latter part of 1980s.

It is estimated that more than 500,000 new cases are diagnosed each year; approximately 15–20% of lung cancer patients have small cell lung cancer (SCLC) and the other patients have non-small cell lung cancer (NSCLC), such as adenoscarcinoma, squamous cell carcinoma, and large cell carcinoma.

Non small cell lung cancer (NSCLC)

Surgery is the main curative treatment for early stage NSCLC (Stages I and II) with a 5-year survival rates of approximately 70–80% in stage I and 50–60% in stage II, but most patients with NSCLC have advanced disease at the time of presentation and are not candidates for curative surgery. Up to the late 1980s, the standard management for this group of patients was conventional external beam thoracic radiotherapy alone. However, the results of radiotherapy alone were disappointing, with a median time to progression less than 6 months, a median survival less than 1 year; the 2-year and 5 year survival rate is in the range of 15–20% and 5% respectively [1].

These poor results have led towards a greater intensification of local therapy, through the use of new radiotherapy techniques, such as three-dimensional conformal radiotherapy (3D-CRT), the use of altered fractionation schemes and the combination with chemotherapy.

Several studies [2, 3] have suggested that local tumor control is a function of the radiation dose delivered, with higher radiation doses resulting in a higher probability of local control and hence prolonged survival. The development of three-dimensional conformal radiotherapy (3D-CRT) techniques has allowed for dose escalation with acceptable levels of morbidity.

Preliminary studies [3] exploring the feasibility of this technique showed that the delivery of up to 100 Gy is safe with predictable toxicity and promising results in terms of survival.

Radical radiotherapy for NSCLC is most commonly given in daily fractions for a total dose of 60–70 Gy over 6–8 weeks. Novel fractionation schedules have been explored with the aim of improving local tumor control and survival without increasing late morbidity.

In hyperfractionated radiotherapy, the dose per fraction is reduced (typically 1.0–1.2 Gy), the number of fractions is increased, with a conventional overall treatment. A phase II study of the Radiation Therapy Oncology Group (RTOG) looking at the optimal total radiation dose with an hyperfractionated schedule, tested total doses between 60 Gy in 5 weeks and 79.2 Gy in 6.5 weeks (dose per fraction of 1.2 Gy, administered twice daily). A dose-response relationship was observed but the greatest benefit was seen with a dose of 69.6 Gy in 5.5 weeks which resulted in 1- and 3-year survival rates of 58 and 20% respectively [4]. However, there is little evidence to support the use of hyperfractionated radiation therapy.

Radiolabelling studies of tumour cell kinetics have shown high potential in vivo doubling times in NSCLC. These studies have suggested a possible role for a very aggressive accelerated radiotherapy course (named CHART: Continuous Hyperfractionated Accelerated Radiotherapy). The rationale is to exploit the potential benefits of both accelerated fractionation (fractions given several times per day with a considerable shortening of the total treatment time, thus decreasing the opportunity for tumor cells repopulation during treatment) and hyperfractionation. In one randomized trial [5], CHART regimen was shown to be superior to conventional radiotherapy in 563 patients with locally advanced NSCLC, with a 24% reduction in the risk of death in the CHART group; CHART also improved local control and disease-free survival.

Although these altered fractionation schedules may be significantly superior over conventional fractionated radiotherapy, long-term local control with radiotherapy alone is poor.

The curative potential of radiotherapy is limited by the failure to control micrometastatic disease present at the time of diagnosis and ineffective sterilization of the primary tumor within the radiation field. It has been recognized for approximately two decades that patients with locoregionally advanced disease required combined modality therapy.

A meta-analysis [6] of 1780 cases in 11 randomized trials showed that cisplatin containing chemoradiotherapy was significantly superior to radiotherapy alone in terms of survival, with a significant gain in median survival time of approximately 4 months over radiotherapy alone. This effect appears to be due to a lower rate of subsequent systemic failure, indicating the ability of chemotherapy to control micrometastatic disease, at least in some patients.
Thus, the combination of platinum based chemotherapy with thoracic radiotherapy has been considered as the standard treatment for patients with unresectable locally advanced NSCLC.

The problem of the sequence of these modalities has not been fully resolved, but there are some significant clinical data encouraging the use of concurrent delivery of radiotherapy and chemotherapy. In the ICGO phase III trial [7], 320 patients with locally advanced NSCLC were randomized to chemotherapy with cisplatin, vindesine, and mitomycin followed by radiotherapy (sequential arm) or concurrent chemoradiotherapy. The response rate for the concurrent arm was significantly higher (84%) than that of the sequential arm (66%), with a median survival time of 16.6 months and 13.3 months respectively. The 2-, 3-, 4-, and 5-year survival rates in the concurrent group (34.6%, 22.3%, 16.9%, and 15.8%, respectively) were better than those in the sequential group (27.4%, 14.7%, 10.1%, and 8.9%, respectively). In the RTOG trial [8] the survival was significantly superior in the concurrent arm (with a median survival time of 17.0 months and a 4-year survival rate of 21%) than in the sequential arm (14.6 months and 12%, respectively). In these trials, acute toxicities such as myelosuppression and esophagitis were greater among patients on the concurrent arm than on the sequential arm. These results were confirmed by the RTOG 94–10 trial [9], in which 611 patients were randomized to receive induction chemotherapy (cisplatin and vinblastine) followed by standard radiotherapy (60 Gy) versus the same chemotherapy and concurrent radiotherapy starting on day 1 versus hyperfractionated radiotherapy and concomitant cisplatin and oral etoposide.

In the 1990s, several new chemotherapeutic agents were developed, such as irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine. The combination of platinum and these new agents is more effective than the old-generation combination chemotherapy for metastatic NSCLC. However, these new agents could not be combined with concurrent radiotherapy at the full dose.

There are no data from large phase III trials comparing sequential chemoradiotherapy using full-dose new-generation chemotherapy with concurrent chemoradiotherapy using reduced-dose new generation chemotherapy and, at this time, no confirmatory data concerning the addition of induction chemotherapy or consolidation chemotherapy to simultaneous radio-chemotherapy.

Regarding the currently-available evidences for the treatment of elderly patients affected by advanced NSCLC the best treatment is still debated. A comprehensive geriatric assessment is recommended to better define prognosis and to predict tolerance to treatment. With the current evidences, single-agent chemotherapy with a third-generation drug (vinorelbine, gemcitabine, a taxane) should be the recommended option for non selected elderly patients; platinum-based chemotherapy is a reasonable option for fit patients with adequate organ function.

**small cell lung cancer (SCLC)**

Small cell lung cancer (SCLC) is a distinct histological subgroup characterized by very rapid tumor doubling time and an early tendency to metastasize, so that it can be considered as a ‘systemic’ disease. Although it has been recognized as a very chemo-sensitive disease since the early 1970s the overall prognosis remains poor. The main objective of clinical research over the past 20 years has therefore focussed on the optimization of systemic treatment approaches. Nevertheless, uncontrolled loco-regional disease is present in about 80% of patients if chemotherapy is used as the sole treatment; so the addition of loco-regional radiotherapy should help to improve cure rates through an increased local control. However a benefit from prolonged local control is likely to be observed only in patients who have systemic control of their disease or who present with limited stage of disease (LD-SCLC).

A meta-analysis including 13 trials and 2140 patients with LD-SCLC have investigated the impact of radiotherapy on survival, showing the survival benefit of chemo-radiotherapy as compared with chemotherapy alone [10]. The addition of thoracic radiotherapy reduced the risk of death by 14%. This led to a small, but significant increase in the overall 3-year survival from 8.9% (with chemotherapy alone) to 14.3% (with chemotherapy plus radiotherapy, \( P = 0.001 \)). This absolute increase in survival was maintained after 3-4 years. A further meta-analysis confirmed the effect of radiotherapy on survival [11].

Based on this meta-analysis, chemo-radiotherapy is considered to be the standard treatment for LD-SCLC.

In the elderly, the addition of radiotherapy to chemotherapy must be carefully evaluated. The best approach is to design clinical trials that specifically include geriatric assessment to develop active and well-tolerated chemotherapy regimens. Although age is frequently associated with comorbidities and a lower performance status, there is also a tendency to treat elderly patients less intensively. Two reports analyzed the outcome of patients over 70 years of age included in prospective randomized trials for combined modality therapy [12, 13]. Fifty and 88 patients of age ≥70 years were identified. The outcome of these elderly patients was comparable to the majority of the somewhat younger patients treated in these trials. Patients should thus not be excluded from combined modality therapy and a curative intent approach based on age alone.

The meta-analysis of thoracic irradiation did not establish an optimal time schedule for chemotherapy and thoracic radiotherapy.

Two randomized studies investigated early radiotherapy (starting within 3 weeks after the beginning of chemotherapy) versus late radiotherapy (starting 12 weeks after the beginning of chemotherapy). The NCIC trial [14] showed an improved 2- and 5-year overall survival and decreased intracranial relapses with early thoracic irradiation (40 Gy) concomitant with cisplatin/etoposide chemotherapy. The Japanese Clinical Oncology Group [15] randomized patients to four cycles of cisplatin/etoposide chemotherapy with either concomitant or sequential hyperfractionated thoracic radiotherapy (2 × 1.5 Gy, total dose 45 Gy) or the same radiation after completion of the chemotherapy. Median survival was significantly longer for patients in the concomitant arm (27.2 months vs. 19.5 months).

Regarding the treatment schedules of combined treatment, chemotherapy has evolved from first-generation schedules...
based on cyclophosphamide and doxorubicin, to second generation schedules based on cisplatin and etoposide, which didn’t increase lung toxicity of concurrent radiotherapy.

Further, because of the high incidence of CNS metastases, prophylactic cranial irradiation (PCI) needs to be strongly considered in the currently therapy of small cell lung cancer. A recent meta-analysis [16], using individual data on 987 patients with SCLC in complete remission who took part in seven trials that compared PCI with no PCI, demonstrated an absolute increase in the 3-year overall survival of 5.4% by the use of PCI. Thus, PCI in patients who have achieved a complete thoracic response may further contribute to survival independently from thoracic radiotherapy.

conclusions

While multimodality therapy approaches have allowed us to ameliorate, the current results, nevertheless, indicate an unsatisfactory status. Therefore, all efforts must be continued to treat patients whenever possible on innovative clinical research protocols with a goal of further improving treatment outcomes for the large number of patients affected with this disease.

references