Journal of Oncological Sciences xxx (2018) 1–4

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

Treatment of locally advanced, unresectable or medically inoperable stage III non-small-cell lung cancer; the past, present and future of chemoradiotherapy

Zuleyha Calikusu [a, *], Pelin Altinok [b]

[a] Acibadem Mehmet Ali Aydinlar University, Acibadem Adana Hospital Department of Oncology, Turkey
[b] Bezmialem Vakif University Radiation Oncology, Adnan Menderes Bulvari, 34093 Fatih Istanbul, Turkey

ARTICLE INFO

Article history:
Received 20 October 2017
Received in revised form
4 January 2018
Accepted 19 January 2018
Available online xxx

ABSTRACT

We aimed to review the development of the chemoradiotherapy options used in the treatment of locally advanced, unresectable or medically inoperable Stage III non-small-cell lung cancer (NSCLC) patients with this review. There are many differences about extent and localization of disease for locally advanced stage NSCLC. The optimal management depends upon multiple factors, including the specific combination of tumor (T) and node (N) staging parameters, the potential to achieve a complete surgical resection of all disease if indicated, and the patient's overall condition and preferences. Chemoradiotherapy has always been the cornerstone of treatment of locally advanced NSCLC and techniques have significantly advanced over this time. Radiation oncology needs to develop the new techniques to improve their survival and the toxicity associated with treatment.

1. Introduction

Locally advanced Non-Small-Cell Lung Cancer (NSCLC) accounts for approximately one fourth of all new lung cancer cases. Locally advanced NSCLC remains a complex and heterogeneous disease with evolving treatment approaches. Concurrent chemoradiotherapy (CCRT) has been the standard treatment for patients with unresectable stage III NSCLC.[1–3] The addition of chemotherapy to thoracic radiation improves overall survival (OS), and CCRT appears to offer superior outcomes when compared to sequential therapy. In patients who received cisplatin-based chemotherapy with radiation, there was a 30% reduction in 2-year mortality compared to radiation alone. Using standard traditional radiation doses and techniques, survival rates of 40%, 15%, and 5% were achieved at 1, 2, and 5 years, respectively.[4–6] Recent technological advances in RT and novel chemotherapeutic approaches have provided preliminary data for further improving clinical outcome while minimizing the morbidity associated with the therapy.[5] We reviewed the recent development of chemoradiotherapy in the treatment of stage III NSCLC in this review.

2. The past

Before 1990s, definitive radiotherapy (RT) alone was the mainstay of treatment of the locally advanced, unresectable or medically inoperable NSCLC. RTOG 7301 phase III randomized study found that 60 Gy is the most tolerable and optimal dose with better tumor response offering a better intrathorasic control as well as survival.[7] During the early 1990s, however, as the deaths from distant metastasis were still high, the quest of multiple randomized phase III studies shifted from the standard radiotherapy alone to adding systemic therapies to the radiation. CCRT became as standart.[2–6]

In the 1990s, the predominant RT technique for treating locally advanced lung cancer was two-dimensional. Progress in technology in imaging especially with modern multisliced computarized tomography has led to three-dimensional conformal RT (3DCRT) approach. The widespread use of 3DCRT provides a significant advantage over two dimensional radiation: conformal beam design and the ability to manipulate beam geometry and weighting through the planning process improves coverage of the tumor target, and decreases the dose to normal tissue.

Cooperative group studies dating back as far as 25 years established that sequential chemotherapy and radiation therapy modestly improved survival over radiation therapy alone. With the better treatment planning systems and developments in the image guidance during radiotherapy, the use of intensity-modulated RT (IMRT) has been increasing in frequency over the past two decades.

* Corresponding author.
E-mail addresses: zuleyha2004@hotmail.com (Z. Calikusu), plnaltnk@gmail.com (P. Altinok).

Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2018.01.003

In contrast to 3DCRT, IMRT is inverse planned. The use of IMRT results in a more conformal plan than 3DCRT, thus reducing the exposure of surrounding normal tissue to high doses of radiation.[8,9]

3. The present

Despite multimodality treatment, the prognosis for unresectable stage III NSCLC remains poor, with five-year OS rates of approximately 15%.[10,11] Therefore interest exists in developing newer treatment paradigms such as radiation dose escalation and integrating newer systemic therapies to radiotherapy.

3.1. Concurrent chemoradiotherapy

The addition of chemotherapy to radiation has been the subject of many prospective trials and several meta-analyses. 1995 meta-analysis of stage III NSCLC examined 1887 patients from 14 trials, found that there was a significant reduction in mortality rates with the addition of chemotherapy to radiation. Combined therapy with both cisplatin-based and noncisplatin-based groups were better than radiotherapy alone. For cisplatin-based group, 1 and 2-years reduction in mortality was 24% and 30%, respectively whereas it was 5% and 18% for the noncisplatin-based group.[12] The first large-scale trial to demonstrate a survival benefit with sequential chemoradiation therapy compared with standard RT alone was conducted by the CALGB.[13]

After the trials supporting survival advantage with sequential chemotherapy, CCRT was also questioned under the knowledge of chemosensitization. RTOG 9410 trial was the key study showing higher survival and higher response rate with CCRT.[14] Several trials clearly demonstrate an OS advantage for the use of CCRT as opposed to the sequential use of chemotherapy followed by thoracic RT.[15] The absolute survival benefit was 4.5% at 5-years with the concurrent approach.[11] The use of concurrent, rather than sequential, chemotherapy with thoracic RT appears to improve OS, at the cost of increased acute toxicity. So, induction chemotherapy should be used for bulky diseases which is the issue for radiation portals in terms of protecting normal tissues.[16]

Although CCRT is the standard, the best chemotherapy regimen in CCRT is not well defined. The two chemotherapy regimens that have been most commonly used in the United States are the cisplatin-etoposide and carboplatin-paclitaxel regimens during CCRT.[17] Cisplatin regimens found to be better than carboplatin regimens and offer a higher response rate.[18–20] But grade 3 or higher adverse effects were less with paclitaxel-carboplatin regimen. Third generation chemotherapy regimens were mostly found to be non-inferior but generally more toxic.[21,22]

The choice of a particular regimen is often made on the basis of secondary factors, such as cost, logistical convenience, ease of administration, toxicity profile, patient preference, and physician experience. Induction chemotherapy appears to reduce the number of distant relapses, which translates into a modest benefit in survival. Further studies are necessary to fully define the optimal administration of current chemoradiation with or without induction or consolidation chemotherapy.

3.2. Molecular-targeted combined modality therapy

Molecular-targeted therapy is a novel strategy born from our increasing understanding of the underlying pathways and key molecules. The addition of antiangiogenics has not improved outcomes. The RTOG phase II trial (RTOG 0324) administered weekly cetuximab with carboplatin and paclitaxel to patients with stage III disease who were receiving concurrent chemoradiation therapy and reported a response rate of 62% and a 24-month OS of 49.3%.[23] A randomized trial conducted by the Eastern Cooperative Oncology Group added thalidomide to concurrent or sequential chemoradiation did not show any benefit.

Bevacizumab, the monoclonal antibody to the vascular endothelial growth factor receptor was also used with chemoradiation. It provided longer overall and progression free survival (PFS) with higher response rates but grade 3 or worse toxicity was more frequent and tracheoesophageal fistula formation was the major problem. So, routine concurrent clinical use of Bevacizumab with radiation is not recommended.[24,25] Bevacizumab, has also been added to chemoradiation in a phase 2 study that also incorporated an EGFR TKI and escalated radiation dose.[26] There was no improvement over standard therapy.

3.3. Immunotherapy and chemoradiotherapy

Given preclinical evidence suggests that chemotherapy and radiotherapy may up-regulate PD-L1 expression in tumor cells.[27–29] Low doses of fractionated radiotherapy led to PD-L1 upregulation on tumor cells in a variety of syngeneic mouse models of cancer. Mechanistic investigations showed that IFNγ produced by $CD8^+$ T cells was responsible for mediating PD-L1 upregulation on tumor cells after delivery of fractionated radiotherapy. In a phase III trial, over 700 patients with unresectable stage III NSCLC without progression after at least two cycles of platinum-based chemoradiotherapy were randomly assigned to the programmed death ligand 1 (PD-L1) antibody durvalumab or placebo in a 2:1 ratio.[30] The benefit in PFS with durvalumab was observed irrespective of PD-L1 expression before chemoradiotherapy. The results demonstrate efficacy and tolerability of durvalumab for treatment of unresectable stage III NSCLC in patients who experience an objective response or stable disease following completion of chemoradiotherapy.

3.4. Other treatment approaches

Multiple image guided ablative techniques are being developed for use in patients with primary nonsmall cell lung cancer (NSCLC) or oligometastatic pulmonary lesions in whom surgery is not an option. Radiofrequency ablation is the most studied technique, but other approaches under development include microwave ablation, laser ablation, cryoablation, and irreversible electroporation.

3.5. Improving the radiation

The standard dose and fractionation regimen of RT with chemotherapy for stage III NSCLC remains 60 Gy in 30 daily fractions over 6 weeks. Retrospective analysis of 7 prospective RTOG trials showed higher biologically effective dose (BED) results better outcomes. Increasing dose intensity turns out increased local control and better survival.[31] Phase I-II dose escalating studies demonstrated 74 Gy as the maximum tolerated dose.[32] But RTOG 0617 Phase III trial comparising high dose 74 Gy with standart dose 60 Gy in the modern radiation technique era, found 74 Gy was worse than 60 Gy in terms of overall survival and toxicity. And also Cetuximab did not effect survival.[33] Mature 5-year follow up data of this trial supported the same results.[34]

Hyperfractionated radiotherapy is the way to give higher radiation doses over the same period of time. Radiation is given 2 times per day with 6 h intervals. Results of RTOG 8808 and RTOG 9410 trials showed no advantage of hyperfractionated regimens over the standart courses.[35] Continuous hyperfractionated accelerated radiotherapy (CHART) is applied in 12 consecutive days, 1.5 Gy per fractions, three times per day to a total dose of 54 Gy.[36] CHART significantly improves overall survival at 2-years, but the largest

Please cite this article in press as: Calikusu Z, Altinok P, Treatment of locally advanced, unresectable or medically inoperable stage III non-small-cell lung cancer; the past, present and future of chemoradiotherapy, Journal of Oncological Sciences (2018), https://doi.org/10.1016/j.jons.2018.01.003