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Outcome of patients with locally advanced Non-small cell lung cancer treated with sequential chemotherapy and radiotherapy in Duhok/ Iraq

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Abstract

Background and objectives: About one third of non-small cell lung cancer patients present with locally advanced unresectable disease. The overall survival and progression free survival evaluated of patients with stage IIIA and B non-small cell lung cancer treated with sequential chemotherapy and radiotherapy. The aim of the study was to evaluate the efficacy of sequential chemotherapy and radiotherapy in advance non-operable non-small cell lung cancer. **Methods:** This retrospective study included 45 patients with advanced non-small cell lung cancer diagnosed between May 2014 and May 2017 treated with sequential chemotherapy and radiotherapy. All patients were treated at Azadi Cancer Centre, Azadi Teaching Hospital, Duhok with at least 4 cycles of chemotherapy then sent to radiotherapy in other centre to complete their planned treatment protocol. **Results:** This study showed that squamous cell cancer was the most common histological sub-type. The overall survival of patients treated with sequential chemotherapy and radiotherapy was 19.6 months (95% confidence interval 13.5–27.8, 95% confidence interval). The median progression free survival time was 11.1 months (95% confidence interval; 8.6–13.7 months). Over all chemotherapy and radiotherapy tolerated well in most of the patients with mild adverse effect. **Conclusions:** Sequential chemotherapy and radiotherapy is a valid option of treatment in inoperable non-small cell lung cancer. This mainly helpful in area with limited resources for radiotherapy. These results provide hope and support of using sequential chemotherapy and radiotherapy in advanced stage lung cancer ineligible for surgery.

Key words: Chemoradiation, Chemotherapy, Non-small cell lung cancer, Radiotherapy.

Introduction

Lung cancer is the major cause of cancer death in men and the second leading cause of cancer death in women worldwide[1]. The main cause of lung cancer is tobacco smoking. In Kurdistan, bronchogenic cancer is increasing in incidence and it was the most prevalent cancer in male after haematological malignancy between 2007-2009[2,3]. About 30% of patients with non-small cell lung cancers (NSCLC) present with unresectable locally advanced disease[4,5]. Treatment generally consists of chemotherapy (CHT) concurrently with thoracic radiotherapy (RT), starting after the second cycle of CHT. However, in daily practice this is not always applicable and about 80% of patient are treated otherwise[6]. Sequential CHT (SCRT) and RT recommended in patients who are unfit to receive concurrent chemoradiation (CCRT) or when the RT planning target volume is considered too large. Observational studies conducted in Belgium and The Netherlands showed that older age and advanced N-stage were significantly associated with higher rate of using SCRT[7]. The prognosis of these patients is poor, stage IIIA and IIIB have a five year survival rates of 18% and 8%, respectively[8]. Combining CHT with RT in the management of advanced stage NSCLC demonstrated a survival benefit when compared to thoracic RT alone. Several phase III Randomized trials showed an increased median survival from 10 months to approximately 13 months with two cycles of platinum based CHT administered before thoracic RT[9,10]. This combination of CHT and RT shows a theoretical advantage based on several interaction mechanisms between CHT and RT. The CHT minimizes the risk of distant metastasis while RT provides loco-regional control of the disease. In addition, chemotherapeutic drugs act as radiosensitizers by increasing the effect of RT[11].

Results obtained from clinical trials exploring lung cancer treatment are not always consistent with the clinical practice in real life. The aim of the study was to assess the efficacy and survival benefit of using sequential chemo-

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therapy and radiotherapy in patients with unresectable Stage III NSCLC ineligible for surgery in Duhok governorate/Kurdistan Province/ Iraq.

Patients and Methods

This retrospective study included patients treated at the Azadi Cancer Centre, Azadi Teaching Hospital, Duhok General Directorate of Health.

All patients or their carers participating in this study signed informed consent to have their data collected and used for research. Duhok General Directorate of Health Ethics Committee approved this study (Ethics Approval Reference Number: 10052017-4). Forty-five patients with locally advanced inoperable NSCLC stage IIIA and B treated with SCRT from May 2014 to May 2017. All cases have consultation at thoracic surgery department, decided to be inoperable, and referred to medical oncology department by consultant thoracic surgeon.

All patients treated with SCRT, 2-4 cycles of CHT given before RT. Radiotherapy started within 3-6 weeks of the completion of CHT (after the patient had recovered from the toxicity of CHT). After RT was completed, two cycles of CHT could be administered if patients' have active disease. A maximum of 6 cycles of CHT permitted for each patient.

Most patients received at least 4 cycles of CHT. Twenty-three patients treated with 4 cycle of carboplatin (Area under the Curve, 6 on day 1) plus paclitaxel (175 mg/m2 on day 1) every 21 days. Five patients received 4 cycles of carboplatin (AUC 6 on day 1) plus pemetrexed (500 mg/m2 on day 1) every 21 days. Four patients were treated with 4 cycle of carboplatin plus gemcitabine (175 mg/m2 on day 1) every 21 days, six patients received 4 cycles of cisplatin (60 mg/m2 on day 1) plus pemetrexed (500 mg/m2 on day 1). Three patients received 4 cycles of cisplatin (60 mg/m2 on day 1) plus gemcitabine (1000 mg/m2 on day 1 and D8), two patients received 4 cycles of cisplatin (60 mg/m2 on day 1) plus navelbine (30 mg/m2 on day 1 and D8). One patient received 4 cycle of cisplatin (60 mg/m2 on day 1) plus docetaxel (60 mg/m2 on day 1) every 3 weeks; two patients received 4 cycles of cisplatin (60 mg/m2 on day 1) plus paclitaxel (175 mg/m2 on day 1 and D8). All patients underwent radiation therapy in one of three centres Sulaymaniyah Zianhwa, Elazig Turkey Medical Park and Erbil Radiation centre (40-55 Gy, in daily fractions of 1.8 Gy, 5 days per week).

Patients were included in this study if they followed eligibility criteria: Male or Female with confirmed NSCLC cancer (stage III; inoperable), ECOG 0-2 and adequate bone marrow, renal and liver functions before starting treatment. Patients excluded if they have stage IV disease and patients with liver, kidney impairment and cardiac insufficiency. Forty-five patients closely followed up and included in statistical analysis. Five patients not assessed and excluded from study due to loss of follow up.

Kaplan Meier survival analysis used to determine overall (OS) and progression free (PFS) survivals using Statistical Package for Social Sciences (SPSS version 23 IBM, Chicago, IL). Survival data calculated from the time of diagnosis to the time of progression and/or death or the last follow-up. P-values of ≤ 0.05 were considered significant.

Results

Fifty patients treated with SCRT between May 2014 and May 2017, 5 patients excluded from the analysis due to loss of follow up. Characteristics of the patients detailed are shown in Table (1). Median age, 64 years (range 44–90 years), male/female was 87/14 %; Eastern Cooperative Oncology Group ECOG performance status scale of 0/1/2 were 22, 62 and 16% consecutively. The stages of the patients were Stage IIIA in 13 (29%) and IIIB in 32 (71%) patients. The histological diagnosis was squamous cell carcinoma (SCC) in 30 (67%), adenocarcinoma in 12 (27%), large cell carcinoma in 2 (4%) and adenosquamous in 1 (2%) of the patients.

Thirty patient had biopsy using bronchoscopy, 10 had CT guide biopsy and 5 patients needed to do both procedures to have enough sample for histopathology and molecular study. Patients had CT scan of chest and abdomen plus MRI brain for staging, while only 5 patient needed a confirmation by PET-CT scan to assess for operability. Main presenting symptom was chest pain followed by cough and dyspnoea

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Table (1): Patient characteristics.

Characteristic	No.
No of patients	45
Median age	84±10.2
Range	44-90
Gender	
Male	39
Female	6
ECOG	
0	10
1	28
2	7
Histology	
Squamous cell cancer	30
Adenocarcinoma	12
Large cell and adenosquamous	3
Stage	
IIIA	13
IIIB	32
Smoking	
Non-smoker (passive smoker)	5
Ex-smoker	2
Smoker	38

ECOG: Eastern Cooperative Oncology Group.

Molecular study was not available in central governmental lab, therefore only 12 patients were able to do ALK and EGFR mutation analysis 10 had no mutation for EGFR while 2 harboured mutations. Only one patient was positive for ALK rearrangement. Histopathology sample of 4 patients were tested for PDL1 and only one had positive expression in 75% of the tumor tissue using FDA approved method of detection. ROS1 rearrangement was tested in 2 patients however both were negative, Table (2).

Table (2): Molecular subtype of non-small cell lung cancer.

Molecular testing	Negative	Positive
EGFR	11	1
ALK	10	2
PDL1	3	1
ROS1	2	

ALK: Anaplastic lymphoma kinase.
EGFR: Epidermal Growth Factor Receptor.
PDL1: Programmed death-ligand 1.
ROS: Proto-oncogene tyrosine-protein kinase

Out of 45 patients, 15 (33.3) achieved a complete response, 18 (40%) achieved a partial response, and 12 (26.7) had progressive disease. The median follows up of alive patients was 40 months (range, 19–63 months). Thirteen patients were alive at the time of this analysis. Of these, 6 patients were without evidence of disease progression. The median OS was 19.6 months (95% confidence interval 13.5–27.8 months), Figure (1). The median PFS time was 11.1 months (95% confidence interval; 8.6–13.7 months), Figure (2).

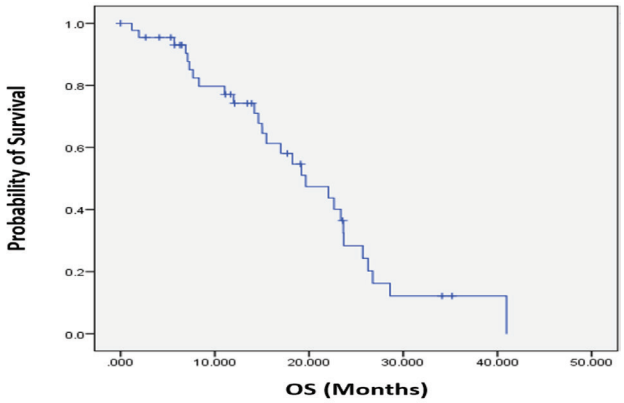

Figure (1): Kaplan–Meier analyses of over survival (OS) in patients who were treated with sequential chemotherapy and radiation therapy.

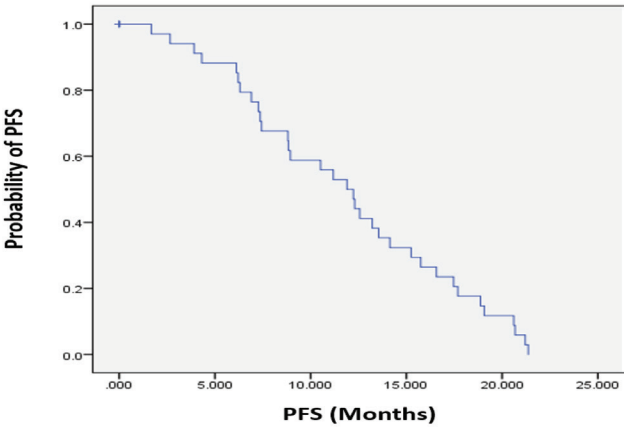

Figure (2): Kaplan–Meier analyses of progression free survival (PFS) in patients who were treated with sequential chemotherapy and radiation therapy.

Patients with SCC showed significantly poorer OS than those with AC (95% confidence interval 16-22 months for SCC compared to 18-48 months for AC); however, this was statistically not significant. There were no statistically significant differences in PFS between AC and SCC.

All patients had at least 4 cycles of chemotherapy before radiotherapy, except one patient (90 years old) who had 2 cycles, he stopped chemotherapy because of poor performance status. Chemotherapy well tolerated in most of the patients. Loss of appetite, grade 2 neutropaenia and fatigability were the most common adverse effect. No patient interrupted CHT because of treatment-related toxicities, except for 2 patients who delayed CHT one week due to febrile neutropenia. There was no Grade 5 toxicity during CHT.

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Discussion

We are living at war-torn region with limited resources for cancer patient treatment. We have previously shown that lung cancer incidence is increasing in Kurdistan Region[12]. However, there are no data about presentation, stage of disease at first diagnosis and outcome of patients with lung cancer in the Kurdistan Region, Iraq. To the best of our knowledge, this is the first paper discussing the current treatment strategy used in this group of patients in this region. Interestingly, in a study conducted by Alrahim, he found that most patients treated with CHT followed by RT and/ or RT alone in 90% of lung cancer patient, while only 10% treated with surgery. This is an indication that lung cancer patient presented at late stage in Iraq[13-14]. Staging conducted by CT scan and MRI brain and 5 patients needed PET-CT to assess for operability. Unfortunately, we did not have endobronchial ultrasound, which is very important to differentiate between stage IIIA operability. However, all cases included in this study have second opinion of cardiothoracic surgeon for operability. This study showed that SCC was the most common histological subtype followed by adenocarcinoma similar to what published in middle and south part of Iraq and to international studies[13-16]. Treatment of stage III inoperable NSCLC patients should involve a multidisciplinary discussion. All patients who were ineligible for surgery should first be considered for CHT plus RT, being either concurrent or sequential. Eric Miller et al., found that multiagent CHT is preferred over single-agent regimens in suitable elderly patients (p-value< 0.001) that resulted in a 21% decrease in the HR for death in patient treated with multiagent compared to single agent CHT. All patients in this study treated with doublet CHT that support good survival outcome. This study confirms that the SCRT is a good option of treatment for patient with inoperable advanced NSCLC. There is a long waiting list for RT in our local referral centres that makes it difficult for our patients to start RT concurrently with CHT. In addition, difficulties are raised to arrange CHT in different centre in another city with different medical oncologist to start concurrent chemotherapy and radiotherapy. Hence, medical oncologists have to arrange for RT appointment and then treat cancer patient with 4 cycles of CHT. In a large retrospective study conducted in Taiwan showed improved survival in patient who were participated in multidisciplinary team management compared to non-participant group[17]. This study shows the importance of collaboration between thoracic surgeons, pulmonologist, radiologist, pathologist, medical oncologist and radiation oncologist to improve patient outcome.

Although, concomitant CRT improves survival compared to sequential treatment in patients with locally advanced NSCLC (increase in median survival of 1-3.4 months), however, such an approach showed higher toxicity than sequential CRT18,19. Femke and his colleagues found that only 20% of patients with stage III A/B NSCLC are not eligible for surgery and been treated with concomitant CRT. This could be for various reasons such as higher risk of acute grade 3-4 oesophageal toxicity in concomitant versus sequential CRT (18%vs. 4%)6. Several studies investigated CCRT versus SCRT to NSCLC[18, 19]. In a meta-analysis, study comparing CCRT with sequential chemotherapy followed by RT of six trials that included 1,205 patients, a significant OS benefit shown with an absolute benefit of 4.5% at 5 years. However, the rates of distant disease progression in the concurrent and sequential arms were similar, 40.6% and 39.5% at 5 years, respectively. In addition, CCRT was associated with a significantly higher rate of grade 3 or 4 oesophageal toxicity compared with sequential chemotherapy and RT, 18% versus 4% by Aupérin et al who showed good OS and PFS with minor adverse effects and lower haematological toxicities. This supports that SCRT significantly have lower rates of toxicity[19]. A retrospective study conducted based on the Netherlands Cancer Registry reported no significant difference in OS for patients age 70 years or older who were treated with CCRT compared with that of patients treated with SCRT[20]. Furthermore, a multicentre retrospective study based on United State National Cancer Database showed that the median OS was significantly higher in elderly patients treated with SCRT than in those treated with CCRT: 20.0 months versus 17.8 months. In addition, SCRT corresponded to a 9% reduction in the risk for death[21].This study showed better OS outcome in advance NSCLC patient with AC compared to SCC, however, this was statistically not significant might be because of small sample size. Our results showed that treatment of advanced stage in-operable NSCLC with

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sequential Chemotherapy and RT in area with limited resources is still a valid option. Additionally, patient treated with SCRT had no severe complication.

This study has few limitations. Patient treated in different RT centres with different protocols. Chemotherapy protocols were dependent on medical oncologist choice with no central decision. In addition to that, the study population was small. Nonetheless, we feel that there are several strengths to be noted. This is by far the first study that includes patients with advanced NSCLC treated with sequential chemotherapy and radiotherapy in Iraq.

Conclusions

Based on our findings, SCRT is a valid option of treatment in inoperable NSCLC. This mainly helpful in area with limited resources for radiotherapy. These results provide hope and support use of SCRT in advanced stage inoperable NSCLC.

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