دراسة دور المعالجة الكيميائية قبل العمل الجراحي في أورام الرئة غير صغيرة الخلايا

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الملخص

خلفية البحث وهدفه: درِسَ إعطاء المعالجة الكيميائية قبل العمل الجراحي لمرضى سرطان الرئة غير صغيرة الخلايا (مرحلةIIIA , IIIB)

مواد الحث وطرائقه: إذْ أُعْطِيَتْ ثلاثة أنظمة علاجية مختلفة ومعروفة عالمياً بفائدتها في علاج سرطانات الرئة غير صغيرة الخلايا.85 مريضاً أُدْخِلُوا بالدراسة التي أجريت في مشفى البيروني الجامعي في حرستا بين الشهر 1 من العام 2009، وحتى الشهر 12من العام 2011.

النتائج: من بين ال85 مريضاً كان هناك 75 ذكراً وعشرة إناث.48 مريضاً كانت أعمارهم أقل من الستين عاما، و58 مريضاً كانوا يعانون من سرطان رئة غير صغيرة الخلايا، شوكية الخلايا. و27 مريضاً كانوا يعانون من سرطان رئة غير صغيرة الخلايا، غير شوكية الخلايا.

أعطيت النظم العلاجية على الشكل الآتي: 50 مريضاً تلقوا بروتوكول سيسبلاتين/جمسيتابين ،11 مريضاً عولجوا بنظام سيسبلاتين / دوسيتاكسيل، بينما 24 مريضاً تلقوا العلاج ب سيسبلاتين /فينورلبين.

عند التقييم بعد 3 جرعات كيميائية، تبيّن بوضوح فائدة العلاج الكيميائي قبل العمل الجراحي في الأورام المتقدمة موضعياً، وعند المرضى أقل من عمر الستين.

وكانت هناك أفضلية بشكل قليل للعلاج بنظام السيسبلاتين والفينورلبين. هذه الدراسة بحاجة إلى عدد أكبر من المرضى لتأكيد هذه النتائج.

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Study of Role of Neoadjuvant Chemotherapy in Non-Small Lung Cancer

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Abstract

Background: Neoadjuvant chemotherapy for patients with non-smell lung cancer was studied before undergoing surgery according to the response.

Methods: 85 enrolled Patients treated from Jan 2009 till Dec 2011 with neoadjuvant chemotherapy. 75 pts males and 10 pts females.48 patients (56,5%) had less than 60 years. 58 patients (68,2%) had Squamous cell carcinoma subtype (SCC) , while the other 27 patients (31,8%) had (Non SCC). All patients underwent pretreatment evaluation at AL BAYROUNI University cancer center. Some patients (32%) had complete mediastinoscopy staging, and all were believed to be poor candidates for up-front surgery because of the bulky disease. Different chemotherapeutic protocols were employed (Gemcitabine/cisplatin) (Docetaxel/cisplatine) and (vinorelbine/ cisplatine). Study end points included resectability, pathologic response, local-regional control,and the best chemotherapy regimen . An exploratory comparison between pathologic response and both histology and age was performed. On the other hand,An exploratory comparison between the three different regimens of chemotherapy was also done.

Results: Of the 85 patients, 26 (30,5%) were deemed surgical candidates after induction therapy however 7 patients of which (8,2%) refused surgery, were 27/85 males and 2/10 females had good downstaging P value (0.0001) and (0.0003) respectively with T downstaging 20/85 (23.5%), and N downstaging 18/85 (21.2%) but T+N downstaging was seen in only 9 patients (10.6%)P value (0,0001).The response to induction chemotherapy was 30/85 patients (35.2%) with one patient only (1.2%)` in a complete response . furthermore, 26/85 patients were in objective response (30.5%) and while 3 patients (3,5%) had a stable disease.Regarding responders' age, there were 18/48 patients (37%) aged 60 years and less, and only 8/37 patients (21.6%) were over 60 years.Depending on response to histology, 21/58 patients (34.5%) of SCC had got a response to preoperative chemotherapy, P value (0,0015), while 10/27 patients (37%) had no SCC,P value (0,0295).50/85 patients (58.8%) treated by (Gemcitabine / Cisplatin) protocol with 15 responders(30%) P value (0,0197),24/85 patients (28.2%) treated with (Vinorlbine / Cisplatin) protocol with 11 responders (45.8%) P value(0.0125) . And finally,11/85 of pts (12,9%) treated by (docetaxel / cisplatin) protocol showed four responders (36.4%) P value (0,0332).

Conclusion: The preoperative chemotherapy gives a good response for a possible surgery in patients with stages IIIA and IIIB NSCLC. this response was better in patients under 60 years , P value (0,0055). With response was better seen in Vinorelbine and Cisplatin arm . However , regarding histology based response, there was no preference.the former results lead us to use neoadjuvant chemotherapy in locally advanced NSCLC,but we still need a larger trials to reach the best protocol.

Background: Non-small cell lung cancer (NSCLC), primarily including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for approximately 80% - 85% of all lung cancers, and approximately two-thirds of NSCLC patients are found to have advanced-stage disease at diagnosis (1,3).

The standard of care for the initial treatment of these patients is a platinum-based, two-drug chemotherapy (2). However, its therapeutic effect is limited and the prognosis of patients with advanced NSCLC remains poor(3,4).

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Stage IIIA and IIIB are very challenging cases because surgery is not possible in most cases, therefore, neoadjuvant chemotherapy seems to be a good choice in these cases in order to reduce both tumor volume and nodal status and consequently downstaging the disease itself (5).

About 40% of lung cancer patient will have a locally advanced stageIII disease confined to the chest (2,4,5,6) . Stage III lung cancer is defined in terms of the TNM staging system described by the American joint committee. In the UK, these patients are considered inoperable. However, there is now evidence to suggest that surgery is a real choice to increase overall survival in non-small cell lung cancer patients(7,8).

Several years ago, Martini suggested that for the majority of patients presented with N2 disease, surgical treatment should be considered seriously(15). More recently, Mountain reported 28% survival for 5 years in patients with locally advanced disease treated by surgery (11). In these series of stage IIIA patients, those with /n2 disease had a significant poorer 5 years survival 21% than those with T3, N0, or N1 disease 39%. However, overall in this group of patients, surgery appeared to offer a long term survival. Although even in completely resected patients, overall survival still around 30%.

The disappointing results for the surgical treatment in stage III non small cell lung cancer patients had led to considerable efforts to investigate the role of chemotherapy before surgery (neoadjuvant chemotherapy). The hope is that, by using such approach, it may be possible to eliminate micrometastatic disease and so prolong overall survival rates.

Eastern Cooperative Oncology Group (ECOG) 4599 was the first phase III study that showed a statistically significant benefit in terms of both overall survival (OS) and progression-free survival (PFS) with carboplatin plus paclitaxel (2) .

In our study, we have recruited 85 patients with locally advanced stages IIIA and IIIB disease treated with 3 main protocols (platinium based) and evaluated the response after the end of treatment.

PATIENTS AND METHODS:

Patients:

The study was done at Al-Bairouni university hospital which is a leading center for treatment of cancer in Damascus (SYRIA) from January 2009 till September 2011. All biopsies were reviewed by a reference pathologist and final diagnosis was provided in compliance with published World Health Organization (WHO) Classification of Lung cancer. Age of enrollment was between 30 and 65 years ,any IPI score ,normal liver and renal functions,PS 0,1 and 2 and of course patients were chemonaive. A CT Scan was done at base-line and only patient with measurable lesions were included and all patient signed a written informed consent before treatment. Patients were also evaluated by mediastinoscopy wherever needed to evaluate the tumor bulk and extension at once.

Treatment plan:

Patients were planned to receive 3 courses of chemotherapy with 3 different protocols which means treating them with 3 different arms as follows: the first arm was Cisplatin 75mg/m2 day 1 and Docetaxel 80mg/m2 day 1 repeated every 21 days. The second arm was Cisplatin 75mg/m2 day 1 and Gemcitabine 1gram/m² day 1 and day 8 to be repeated every 21 days, while the third protocol composed of Cisplatin 75mg/m2 day 1 and Vinorelbine 30 mg/m² day 1 and day 8 to be repeated every 21 days.

The enrolled patients were evaluated by CT scan after 3 courses and the responders were refered to surgery.

Baseline and treatment assessment:

Patients underwent a medical history,physical examination,and tumour measurement of palpable lesions as well as lesions assessed by imaging techniques (Computed tomography and positron emission tomogrphy) while ultrasound scans were not permitted. CT Scan was repeated every three cycles and evey thrree months after treatment completion. The treatment responses: complete response (CR), unconfirmed CR (uCR), partial response (PR) stable disease and progressive disease were classified acording the International Workshop NHL Response Criteria published by Cheson et al (13). Progression free survival was defined as the date of first treatment to the date of documented disease progression or death (event) or the date of last follow-up examination (Censored).

Table (1)

Clinical caracteristics of patients at the baseline (n =85)

Median age (range)	58 (30-65)
Sex (male:female ratio)	75/10 patients (88.2%:11.2%)
Ps 0-1	16/25 patients (64%)
Median follow up	3 years
Distribution of patients by protocol	
Cisplatin/Gemcitabine	50 patients (58.8%)
Cisplatin/Docetaxel	11 patients (12.9%)
Cisplatin/Vinorelbine	24 patients (28.2%)

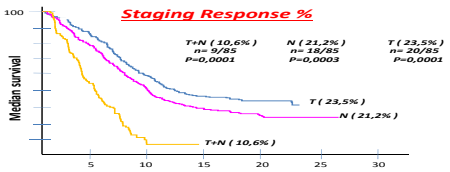
Table (2)

Pathologic subtype

Pathologic subtype	number	percentage
Squamous cell carcinoma	58	68.2%
Non-squamous cell carcinoma	27	31.7%

Results:

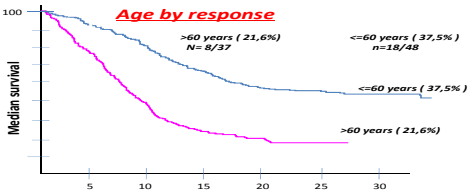
This study was carried out on 85 patients diagnosed with non-small cell lung cancer with different sub-types, 10 out of 85 were female (8%). patients presented with advanced stages IIIA and IIIB. Patients were randomized to be treated with 3 different arms (Cisplatin with Gemcitabine/Cisplatin with Docetaxel and Cisplatin with Vinorelbine) as mentioned before. Every patient received 3 courses of treatment then evaluated by CT scan after the end of treatment. 20 out of 85 patients showed a response on tumor volume (23.5%) with a P.value 0f 0.0001. another 18 out of 85 showed a response on nodal disease (21.3%) with a P.value of 0.0003 while 9 patients only showed a response of both tumor volume and nodes with a P.value of 0.0001as shown in figure 1.



Time

Figure 1: response by tumor volume, nodal status and both

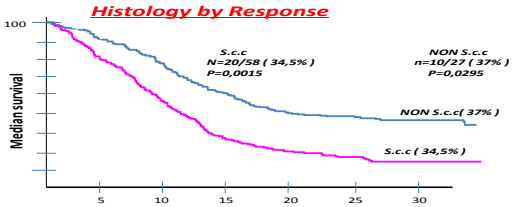
CT scan performed after the 3rd cycle showed a good radiologic response in 26 patients (30.5%), 7 of which (8.2) refused to undergo surgical approach while the rest of patients were ready to be operated.



Time

Figure 2: response rates by age group

Response was shown to better among patients younger than 60 years of age compared with those older than 60 years, 18 out of 48 vs 8 out of 37 patients respectively as demonstrated in figure 20 out of 58 patients (34.5%) with squamous cell type showed a response while 10 out of 27 patients (37%) with non-squamous subtype showed a response as illustrated in figure 3.

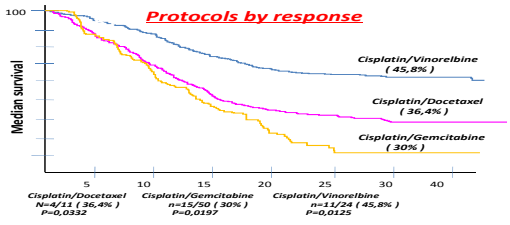


Time

Figure 3: response by histologic subtype

The combination of Cisplatin/Vinorelbine showed a clinical and radiologic benefit in 45.8% of patients. In the other hand, the combination of Cisplatin and Docetaxel showed a response of 36.4% compared with

a response rate of 30% in patients received Cisplatin /Gemcitabine as shown in figure 4.



Time.

Figure 4: Protocols by response

finally, regarding response by sex. Only 3 out of 10 females (30%) included in the study showed a response compared with 27 out of 75 males (36%).

Discussion:

a lot of work was done during the past 10 years in order to increase the overall response and the overall survival as well. However, less work was carried out regarding neoadjuvant chemotherapy which may improve the field of surgery leading to downstaging of patients presenting with locally advanced disease.

NSCLC often presents as hidden onset as the early symptoms are often not typical. At the time of confirmed diagnosis, the condition of patients has often already developed into middle and advanced period so that the effect of surgery and postoperative radiotherapy and chemotherapy is unsatisfactory.

The neoadjuvant chemotherapy can significantly reduce the tumor mass, decrease the micro-metastasis of intraoperative tumor cells and thereby enhance the effect of surgical resection and improve long-term prognosis. Li et al (16) reported the results of neoadjuvant chemotherapy in the treatment of locally advanced NSCLC patients, and showed that the surgical resection rate significantly increased to 89.1%, intraoperative blood loss and operation time decreased, and the 3-year survival rate postoperatively significantly increased. Hu et al (17) administered neoadjuvant chemotherapy before radical resection of pulmonary carcinoma.

Patients with stage IIIA N2 NSCLC exhibit 5-year OS rates of 10–15%. In stage IIIA N2 patients with multistation or bulky disease this rate is only 2–5%. The efficacy of surgical treatment in these cases is controversial. In four previous studies, which included a total of 1,180 patients undergoing surgery, the 5-year OS rates ranged from 14 to 30% . However, these studies used different inclusion criteria, included patients with different prognoses, defined ‘resectable disease’ or ‘marginally resectable tumor’ differently, and used varying CT regimens as induction or adjuvant treatment. Therefore, comparisons must be considered with caution. Despite these limitations, other studies suggest that treatment with cisplatin-based CT improves survival in NSCLC patients.Generally, patients treated with NA-CT exhibit a median survival time of 20 months and a 3-year survival rate of 34% (6,9). This is consistent with the results of the Palka et al study, in which OS was 28 months and PFS was 19.5 months.,(8,10).

The Spanish Lung Cancer Group (13) study included 136 patients with locally advanced NSCLC. Due to the homogeneity of patients enrolled and the geographical location, this is a good reference trial, despite the clear differences in scientific evidence obtained from clinical trials and patient series. The overall complete resection rate was 68.9% among patients eligible for surgery (72% of stage IIIA patients and 66% of stage IIIB patients) and 48% of all assessable patients. In the present study, the overall resection rate for all assessable patients was 85.7%. In the aforementioned trial (11,13), the rate of complete pathological response was 12.9% of 62 completely resected patients, compared with 42.85% in the present study (of 7 patients undergoing surgery, 3 showed complete pathological response in the surgical specimen). However, the fact that the results may have been strongly influenced by the sample size must be considered.

In our study, we concluded 85 patients between 2009 and 2011, 58 patients had squamous cell carcinoma while the remaining 28 presented with non squamous cell carcinoma.In this study, 3 main Platin dependent protocols were used compared with other international studies using only one or two protocols.

Of the 85 patients, 26 (30,5%) were deemed surgical candidates after induction therapy however 7 patients of which (8,2%) refused surgery, were 27/85 males and 2/10 females had good downstaging P value (0.0001) and (0.0003) respectively with T downstaging 20/85 (23.5%), and N downstaging 18/85 (21.2%) but T+N downstaging was seen in only 9 patients (10.6%)P value (0,0001).The response to induction chemotherapy was 30/85 patients (35.2%) with one patient only (1.2%)` in a complete response .

Response was better in patients under 60 years of age the thing that could be attributed to better performance status in those patients leading to good tolerability . furthermore, those patients present with good renal and liver functions and they are able to tolerat the side effects of treatment much better.

Patients received Cisplatin plus Vinorelbine showed better response rates in 11 patients (48.8%) but there are no definitive justification for the former results.

some international trials have shown better response rates than our study which could be attributed to several reasons including better healthcare in western countries as well as inclusion of several subtypes of non-small cell lung cancer and pooling them as one disease. However , our study was the first to evaluate the response according to histologic subtype and age. Though it is an informative study, however, a bigger data is needed to reflect the reality of approaching locally advanced non-small lung cancer in Syria.

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