Review

Stage IIIA NSCLC with limited N2 disease: Induction chemotherapy and reseption or surgical treatment and adjuvant chemotherapy?

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Lung cancer constitutes the most frequent cause of death from malignancy in humans with 160.000 deaths registered annually[1] in the USA and more than one million worldwide[2]. Approximately 85% of the annually diagnosed cases relate with NSCLC with low overall 5-year survival rate (<15%). Thirty percent of the patients with NSCLC and 10% of the total number of patients with lung cancer estimated with locally advanced disease of stage III_A due to the existence of N2 disease.

This heterogeneous group of patients is located in the marginal area between the operable stages I and II and the inoperable stage IIIB, and it is characterized from 5-year survival rates that vary from 13-23%[3]. The therapeutic options for the management of these patients were always a subject of controversy[4]. With the term "limited N2 disease" (minimal N2 disease) we indicate the patients with lung cancer and metastasis in only one group of unilaterally mediastinal lymph nodes without rupture of their capsule and extension in the surrounding soft tissues. These patients present the highest survival rate after complete surgical excision of the disease, a fact that is clearly defined from the term "surgical N2 NSCLC disease"[5].

Despite the implementation of chemotherapy in stages I to IIIA, approximately 60% of the patients relapse and ultimately die even after complete resection of the existing macroscopic disease. In ¼ of these cases the recurrences are local and in the remaining distant or a combination of local and extra thoracic, with the brain, the bones, the adrenal glands, and the contralateral lung to be the most common sites of metastases.

The presence of subclinical micro metastases during the period of primary tumor resection is the most likely cause of relapse. As a consequence, the use of chemotherapy as neoadjuvant or adjuvant chemotherapy has been found to improve the survival of patients with resectable NSCLC. Moreover, the use of combined adjuvant chemotherapy and radation is a good option in the multimodal treatment approach of patients with NSCLC stage IIIA (N2)[6].

The current options in the treatment of resectable NSCLC are: (a) neo-

adjuvant chemotherapy plus surgery (b) surgery adjuvant chemotherapy, (c) neo-adjuvant therapy (chemotherapy plus radiotherapy) followed by surgery and (d) surgery followed by adjuvant chemo-therapy. In this article we will refer to options (a) and (b) and will compare the results between them.

NEOADJUVANT CHEMOTHERAPY

Advantages of neoadjuvant chemotherapy are: (1) it is well tolerated because it is not administrated in patients recovering from surgery as the adjuvant chemotherapy, (2) the reduction or elimination of nodal mediastinal disease (N2→N1→N0) resulting in the downstaging of the disease or the sterilization of the mediastinum, (3) the early destruction or prevention of the micro-metastases, (4) the in-vivo monitoring of the sensitivity to chemo-therapeutic drugs and (5) neo-adjuvant chemotherapy can reduce the tumor volume. Disadvantages are: (1) the occurrence of complications from drug toxicity, (2) the forced delay in the application of the surgery and (3) the resulting increase in surgical morbidity and mortality after the administration of preoperative chemotherapy.

The induction chemotherapy constitutes a very good model for the study of new medicines, because the tumor remains unaffected from other interventions. As a consequence, the drugs reach their target in high concentrations with a uniform way via the intact, from surgical lesions or radiotherapy, capillary network. With that way, the precocious management of micro-metastases and the easier administration of capable doses of chemotherapy are achieved because the clinical condition of the patient is good and unaffected from external factors as the surgical operation and the radiotherapy. The aim is the downstaging of an initially inoperable tumor and its subsequent surgical management. Main disadvantage of the method on her failure is the potential transformation of a marginal operable tumor in inoperable due to the time delay in the potential application of the surgical approach.

The decade of 90s, 4 randomized studies were designed and established, aiming at the comparison of the combination neo-adjuvant chemotherapy and surgery to plain surgery for the management of operable NSCLC STAGE IIIA (N2). The first two[6,8] were conducted in relatively small sample of patients and showed supremacy of the combination neo-adjuvant chemotherapy plus surgery to plain surgical treatment with regard to the total survival. The third study (Japan Clinical Oncology Group) was terminated prematurely, without showing statistically significant difference between the two arms. The fourth and larger study was established in France, incorporated patients of stages I, II and IMA and showed superiority of neo-adjuvant chemotherapy plus surgery to plain surgical therapy.

The studies from Roth et al were established in the University of Texas M.D. Anderson Cancer Center[5,6] in 1994 and 1998. From 1987 until 1993, 60 patients either received preoperative three cycles of eyclophoshamide, etoposid and cisplatin, or they were subjected to plain surgery. In the cases of radiological response, three more cycles of chemotherapy were administrated followed from surgery. After the first three cycles of chemotherapy, partial (reduction of the size of mediastinal lymph nodes in the chest CT) or complete (obliteration of preexisting enlarged lymph nodes) response was observed in 35% of patients. The initial medial survival was 64 months for the group of patients submitted to neoadjuvant chemo-therapy, and 11 months (p=0.018) for the group of patients submitted only to surgery. The correspondent three-year and five-year survival rates were 43% and 19% (p=0.048) and 36% and 15%, respectively (p=0.056). Pathological confirmation of the N2 disease was available in the 85% of patients with mediastinoscopy or mediastinal thoracotomy, while in the remainder there was only clinical staging with chest CT. Certain cases concerned T3N0 and T3N1 tumors, while in the patients where surgical resection estimated as incomplete (non-radical), mediastinal adjuvant radiotherapy was selectively administrated.

The eminent "Study from the Barcelona people" was established in 1994 and 1997 in Spain by Rosell et al[7,8]. Moreover, from 1989 until 1991, 60 patients with positive biopsies of lymph nodes for N2 disease, received either three cycles of mitomycin, eyclophoshamide and cisplatin and then were submitted to surgery, or were submitted directly to surgery and then all received mediastinal radiotherapy with 50 Gy. The partial or complete response rate reached the 60%, with initial median survival 20% for the patients received chemotherapy and 5% for the patients subjected to surgery (p<0.001), while the five-year survival was 17% and 0% respectively (p<0.001).

The studies of Roth and Rosssel amazed and at the same time impressed the medical community, while soon they became worldwide known. However, they received, as it was expected, ruthless criticism because: (1) N2 disease was not pathologically confirmed in all the cases, a fact that could lead in possible errors in the therapeutic management, (2) complete pathological response (microscopic obliteration of living cancer cells

in the mediastinal lymph nodes) was observed in low percentage ≤5%, (3) the surgical result was poorer than the usually expected with late survival after surgery only 15% in the study of Roth et al[5,6] and null in the study of Rossel et al[7,8], (4) the number of patients was small, the cases non-homogeneous (the study included patients of stages T3N0 and T3N1), while mediastinal adjuvant radiotherapy was selectively administrated. More important of all is that these two studies constituted the spark for more researchers to begin worldwide similar studies on that particular subject. The larger study of all accomplished from "The French Thoracic Group" and Depierre et al in 2002[9]. The study involved 355 patients of stages IB, II and MIA with pathologic confirmed NSCLC. One hundred and twenty two patients had N2 disease and some of them N2 bulky disease, that is to say lymphatic blocks in the mediastinal larger than 2 cm in the chest CT. The patients received two cycles of mitomycin, cyclophosphamide and cisplatin, while in patients with even partially response either two cycles of chemotherapy were administrated, or they were submitted only to surgery. Mediastinal adjuvant radiotherapy with 60 Gy was selectively administrated to the patients who were finally proved with T3 and/or N2 disease in either arm of treatment.

Curiously, more pneumonectomies than lobectomies were performed and particular 56% in the group of patients that was submitted directly to surgery and 48.5% in the group of patients that was initially subjected to neoadjuvant chemotherapy. The post surgical mortality was 4.5% and 6.7% respectively, without statistically significant difference between them.

Significant clinical response was observed in 64% of the patients, while only 6% of the patients developed aggressive disease. The overall survival was 37 months for the patients subjected directly to surgery, while the 4-year survival was 44% for the patients submitted to chemotherapy and 35% for those submitted to surgery. Statistically was found that only the patients of stages I and II benefited from the administration of neoadjuvant chemotherapy (p=0,027), but with increased percentage of postoperative mortality: 10% in the arm of chemotherapy and 4.5% in the arm of surgery.

A meta-analysis[10] based upon 7 trials involving 988 patients suggested that neoadjuvant chemotherapy improved survival with a HR of 0.82 (95% CI 0.69-0.97), equivalent to an absolute benefit of 6% at 5 years. There was also a benefit by stage: stage IA +4%, stage IB: +6%; stage II-III: +7%, but there was not any difference between the type of platinum-containing regimen and the type of adjuvant treatment (chemotherapy or radiotherapy). When the mature results of the European Intergroup trial added to the previous meta-analysis, a shift of the hazard ratio to 0.87 observed with loss of the significance of the improvement in outcome.

In a recent meta-analysis of 10 trials using pooled data[11], a marginal survival benefit of adding platinum-based neoadjuvant chemotherapy in respectable IIIA NSCLC patients treated with surgical resection and adjuvant chemotherapy was demonstrated (HR=0.81, 95% CI: 0.67-0.97). However, this was a pooled-data metaanalysis in heterogeneous populations treated with various regimens of platinum-based chemotherapy and there were no specific data regarding the subset III_AN_2.

NEOADJUVANT CHEMOTHERAPY WITH 3rd GENERATION DRUGS

From 2000 and then, in the literature are published studies concerning the administration of neoadjuvant chemotherapy with the newer, third generation, drugs such as gemcitabine, paclitaxel and doxetaxel. In some studies the number of the patients recruited is large such as: (1) The European Organization for Research and Treatment of Cancer (EORTC) 08941 composed in 2000 with 47 patients[12], (2) The Swiss Group for Clinical Cancer Research (SAKK), composed in 2003 with 90 patients[13], (3) De Marinins et al, 2003[14], (4) (EORTC) 8958, composed in 2003 with 52 patients[15], (5) The Italian Lung Cancer Project Observation Study, composed in 2003 with 129 patients[16], (6) (EORTC) 08984, composed in 2006 with 46 patients[17], (7) The Spanish Lung Cancer Group (S9901), composed in 2007 with 136 patients[18].

It seems that the most important predictor in these studies is the mediastinal downstaging, while the most effective regimens with acceptable toxicity included cisplatin and gemcitabine. In conclusion, it was shown that the neo-adjuvant chemotherapy with modern drugs in patients with stage III_AN_2 NSCLC is practically feasible and useful in the early prognosis with acceptable toxicity. The data from 7 studies advocate that the median survival ranged from 15.8 to 27.6 months, while Phase III studies with the recruitment of large numbers of patients are required for the export of safe conclusions[19].

THE ROLE OF SURGICAL THERAPY IN STAGE MIA (N2) NSCLC

The surgical treatment applied after neo-adjuvant che-

motherapy is associated with increased 30-day morbidity and mortality, ranging from 8 to 12%[20,21], while pneumonectomies, usually right, account for the 85% of the deaths, with the most common causes of bronchopleural fistulas and ARDS[22]. This led to the need for improved methods of anesthesia primarily by reducing the quantity of fluid administered perioperatively and measures to prevent barotrauma, including implementation of specific surgical tecnniques to protect the bronchial stump (avoidance of bronchopleural fistulas) with coverage by flaps that maintain their own blood supply such as the intercostal muscles, the diaphragm and the major omentum.

In contrast with the results of the preoperative staging, a part of patients either during the operation or at the final pathologic examination are proved to have unexpected N_2 disease. About 25% of all patients submitted to thoracotomy are found to have unexpected N2 disease [23L]. Then, if the complete resection is feasible, curative thoracotomy should be proceeded with complete lymph node dissection or systematic sampling. The 5-year survival rate after complete resection ranges between 14%-30% with the best results seen in patients with minimal N2 disease[23,26].

Patients submitted to lung lobectomy or bilobectomy showed statistically significant longer survival than the patients who underwent pneumonectomy, longer disease-free survival with five-year survival rates 27% and 12% respectively. When the primary tumor is on left upper lobe of the lungs with infiltration of the lymph nodes at the aortopulmonary window and the para-aortic area, the 5-year survival averages 40%. About 27% to 36% of patients will have skipped metastatic disease[27]. Lymph node dissection or lobe-based systematic lymph node sampling is essential for accurate staging. Also, many researchers put the dilemma whether should be operated only those patients who have sterilized mediastinal lymph nodes, as this is the most important factor in improving survival.

Finally, typically referred to the Guidelines of the American College of Chest Physicians in September 2008 that pneumonectomy is contraindicated after the administration of induction chemotherapy. It is noteworthy that many patients studied had also received preoperative radiotherapy.

ADJUVANT CHEMOTHERAPY- POSTOPERATIVE CHEMOTHERAPY

The adjuvant chemotherapy aims to the delay or cancellation of disease relapse after successful resection surgery. The first studies were designed in the decade of 80's (before the use of platinum) and failed to show a survival benefit from the administration of plain adjuvant chemotherapy or in combination with adjuvant radiotherapy. The small number of the patients involved and the rather ineffective chemotherapeutic drugs uses at that time, which acted with high toxicity and required increased costs are considered as the main causes of failure. In 1995, the results of a large meta-analysis of a total of 4357 patients from 52 studies were announced. The main finding reported was an increase in the five-year survival rate by 5% for the adjuvant chemotherapy based on platinum (benefit from 1% to 10% HR = 0.87, P = 0.08 and 95% CI) and 13% reduction of the probability of death compared with only the surgery[28].

Prominent studies involving the administration of cisplatin in the chemotherapeutic regimen after 2000 were: 1) Scaliotti GV et al recruited 1209 patients in 2003[29], 2) Waller D et al recruited 381 patients in 2004[30], 3) Douillard JY et al recruited 224 patients in 2006 (ANITA trial)[31] and 4) Le Chevalier T et al recruited 1867 patients in 2008[32], which was the largest (IALT trial). In 2006, the results of the study LACE fLuna Adjuvant Cisplatin Evaluation)[33], a large pooled analysis of five studies, the ALPI[34], ANITA[31], BLT[25], IALT[32] and JBR10[35], were notified. A total of 4584 patients were recruited with 25% stage IIIA (N2) patients, while ail patients were postoperatively monitored for at least five years. The survival hazard ratio was calculated as HR = 0.084 for the group of patients submitted to adjuvant chemotherapy (P <0.001) which was reflected in 5.5% five-year survival benefit (5.8 ± 1.6%) with contemporaneous statistically significant prolongation of the disease free survival (DFS).

The effectiveness of the various platinum-based drugs of the administered chemotherapy estimated without heterogeneity between the studies, while the survival benefit varied depending on the stage of disease, ie: HR=1.40 (IA), HR=0.93 (IB), HR=0.83 (II), HR=0.83 (III). It seemed that the chemotherapy performed better in the patients on good performance status, mainly in stages II and IIIA and in selected patients of stage IB, while survival was not associated with gender, age, histological type and type of lung resection (lobectomy or pneumonectomy). Also, it waw shown that the 4 cycles with vinorelbine and cisplatin were marginal superior compared with other medical regimens.

Usually, combinations of platinum with another agent, such as vinorelbine, gemcitabine or paclitaxel, are used. Questionable remain the ideal number of the chemother-

apy cycles, the use of non-platinum based combinations and the potential place of the new agents. Certainly, always significant is the balance between the benefit from the chemotherapy, its toxicity and the cost. The carboplatin can be used instead of the classical platinum, without any substantial difference in the efficiency. Platinum has slightly better efficacy with response rates 30% vs 24%, respectively, as first line treatment of advanced NSCLS, but is more nauseate, nephrotoxic and neurotoxic to the peripheral nerves, while carboplatin is more myelotoxic. Thus, platinum is recommended in young patients with adequate renal function and in acceptable performance status[36].

As for stage IB patients, who admittedly obtain the poorer benefits, there is only one clinical study from Strauss GM et al, reported in 2004[37] which showed a statistically significant survival benefit in patients subjected to adjuvant chemotherapy compared with the patients submitted only to surgery[38].

Besides the classical intravenous administrated chemotherapy drugs, there is the UFT (Uracil-Tegafur), which is taken orally, represents a precursor of 5-flouracil and has been studied mainly in Japan. The largest meta-analysis on the effectiveness of UFT announced in 2005 by Hamada, Tanaka and Ohta[39]. The meta-analysis comprised a total of 6 studies with 2.003 patients in the vast majority with stage I (T^1N^0=1.308 and T^2N^0=674) disease, who suffered mainly from adenocarcinoma. The five and seven-year survival rates with UFT was estimated at 81,5% and 76,5% vs 77,2% and 69,5% for the surgical treatment P=0.011 and 0.001 respectively that could be interpreted into survival benefit at seven years =7% with HR=0.74 (95% CI: 0,61-0.88) and P=0.001.

The largest meta-analysis of patients who received adjuvant chemotherapy and has reported until today, presented in 2007 by Stewart, Burdett, and Tierney[40] on 8.147 patients. It included 30 studies, of which at 15 studies only cisplatin was administrated, in 7 studies cisplatin and UFT and in 8 studies only UFT, while 1.315 patients (17%) presented with stage III disease. The HR was 0,87 (P<0.000001) for the group of patients received chemotherapy, which interpreted in 4% absolute survival benefit for the first five years. The overall five-year survival of patients who received chemotherapy was 64% compared with the respective percentage (60%) of the five-year survival of the group of patients submitted to surgery. The absolute survival benefit in eight years was 5%, with 5,1% improvement in DFS and no statistically significant difference between the administered chemotherapy agents, stage of disease and survival benefit.

The universal contribution of adjuvant chemotherapy is huge. Each year the diagnosis of tung cancer is established in 900,000 people worldwide.

About 85% of these are related with NSCLC, while half of the patients are estimated as having surgical treatment perspective. The 75% of those who will be submitted to surgery will receive adjuvant chemotherapy, which equals to 180.000 cases per year. In other words, the administration of postoperative chemotherapy based on platinum will prevent 7.000 deaths annually.

The ideal treatment of stage III_A NSCLC with limited N2 disease still remains unclear. The multimodality treatment approach with combined chemotherapy and surgery and possible addition of radiotherapy appears to yield the best results. The initial enthusiasm for the induction chemotherapy that emerged from the pioneering studies of Roth and Rosell, who showed improved 5-year survival rate of 15% to 20% compared with only surgery, has clearly declined since in recent studies with modern, third generation, drugs the median survival is around the 22 months (16-28 months)[41]. Most researchers now recommend induction chemotherapy in resectable stage IIIA (N2) lung cancer but without a formal directive from a specific worldwide medical association. Ongoing studies such as the European SAKK-16/00 phase III and RTOG 0229 phase II investigate various regimens of induction chemotherapy with modern chemotherapeutic agents and the potential addition of surgery and radiotherapy. The postoperative chemotherapy, however, is the treatment of choice in resectable NSCLC stage II, IIIA and likely IB (mainly depends on the primary tumor's size >4cm), with 5% five-year survival benefit. Recent studies have shown that the expected new double combination regimens based on platinum can launch the survival benefit, for the surgery alone, even at the level of 8%-15%[36].

Ideally, we could identify somehow in advance the patients who would benefit from the administration of induction chemotherapy (probably patients with micrometastases) opposed to those who will not show any benefit (e.g. resistant to chemotherapy or patients who are free of micro-metastases), so that they are lead directly and without any delay to the operating room to undergo lung resection surgery. The rapid development of molecular biology in the diagnosis and treatment of lung cancer provides expectations that in the near future we will be able to provide more accurate personalized treatment in a disease that despite recent advances still has high mortality.

The answer to the question "which patients will undergo chemotherapy and with which drugs?" seems to be given by the application of methods in the everyday clinical practice which aim to the detection of more accurate prognostic and molecular indicators retraced in the biopsy material or in the excised tumors. The science of molecular biology in the form of "customized therapy" or pharmacogenomics addresses this issue with promising so far results, studying the genetic "profile" of carcinomas[42L,43L]. The analysis of the histological characters of the tumors in the IALT study showed that low levels of the gene ERCC1 (Excision Repair Cross- complementing) prejudice to the good response to chemotherapy based on platinum. Other biomarkers such as the ribonucleotide reductase M1, as well as genomic and proteomic methods are being assessed with regard to their ability to predict the potential postoperative recurrence and the response to chemotherapy[44] in order to administrate molecularly targeted therapy.

In order to answer the main question of our article and to define clearly the treatment of patients with resectable stage IIIA (N2) NSCLC, the "NATS Trial" was designed from the Spanish Oncology Group[45]. It comprises a randomized, phase III study involving 42 centers from 5 European countries and 624 patients with IA, IB, II and IIIA (T3N1) lung cancer (70% in stage I). These patients were classified into three groups and either submitted to surgery, or induction chemotherapy or adjuvant chemotherapy was administrated. The results of this long-awaited study released in August 2009, in San Francisco, California, USA during the 13th World Conference on Lung Cancer (WCLC).

The study showed no survival benefit from the administration of induction or adjuvant chemotherapy compared with only the surgery. Notably, it was found better compliance of the patients to the induction chemotherapy (97% of the patients received 3 cycles of carboplatin and paclitaxel preoperatively) than in adjuvant chemotherapy (66%, n=139, of the patients received adjuvant chemotherapy). After the completion of 5 years, there was no significant difference in time interval with stable, without recurrence, disease (Progression Free Survival – PFS) between the three groups of patients: 38,3% in patients receiving induction chemotherapy, 36.6% in the in patients receiving adjuvant chemotherapy and 34% in patients treated only with surgery. The five-year survival was 46.6% and 45.5% respectively for the patients receiving induction chemotherapy or adjuvant chemotherapy and 44% for patients subjected only to surgery, without statistically significant difference between them, while chemotherapy was generally well tolerated with no significant differences in side effects between the induction and the adjuvant arm.

However, detailed analysis of the prognostic factors did not show any significant difference among the 3 groups. It was proved that the clinical stage II and IIIA (T3N2) patients had the largest survival benefit from the induction chemotherapy compared with the patients in the other two groups. Five-year survivals rates were respectively: 36.6% for the patients received induction chemotherapy, 31% for the patients received adjuvant chemotherapy and 25% for the patients submitted to surgery. The analysts of the NATCH trial continue to assess and analyze the results using biomarkers as prognostic factors. Moreover, it is believed that in the future is unlikely to repeat a similar study in Europe or in US because of great difficulties in recruiting patients in trials with surgical arm.

Professor Peter Goldstraw, president of the IASLC, commenting the results of the NATCH trial said that "this study probably will be the only of its kind regarding the comparison between induction and adjuvant chemotherapy". This study does not support the view that chemotherapy does not work, but it endorses that the candidates to receive chemotherapy should be carefully chosen.

Other prominent commentators have highlighted the fact that although the study failed to demonstrate superiority of the one of the three methods, however, provided some evidence of small superiority of induction chemotherapy. We must not forget that 70% of patients were in stage IA and IB, who generally do not benefit from the administration of systemic chemotherapy (*), while in the arm of adjuvant chemotherapy, many patients did not complete the required 3 cycles of chemotherapy because of postoperative complications. As a result the final conclusions were drawn from only 139 cases, a fact that potentially reduced the benefit survival of the patients of this arm.

Similar results were also revealed and from the study ASCO 2008 of the American Society of Oncology with 10.000 cases from 31 studies, 10 studies regarding induction chemotherapy and 22 studies regarding adjuvant chemotherapy. This study also showed that the precise time of the chemotherapy administration has little effect on the outcome of the patients with resectable NSCLC, in point of morbidity, mortality, disease free interval and overall survival.

In conclusion, we can support the view that for stage IIIA NSCLC with limited N2 disease the better designed

and therefore more reliable studies failed to show a clear statistically significant difference between the available treatments. The radical surgical excision of the tumor, that is to say the removal of the whole macroscopic disease, remains the cornerstone in the multifactorial treatment of stage IIIA lung cancer. In the future, the administration of chemotherapy either as induction or as adjuvant (postoperative) will be determined by the Molecular Biology, which considering the biological aggressiveness of the tumors, will actually perform biological staging of the disease, in addition to the existing anatomical (TNM).

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