REVIEW ARTICLE

Treatment of non-small cell lung cancer (NSCLC)

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ABSTRACT Radical surgery is the standard of care for fit stage I non-small cell lung cancer (NSCLC) patients. Adjuvant treatment should be offered only as part of an investigation trial. Stage II and IIIA adjuvant cisplatin-based chemotherapy remains the gold standard for completely resected NSCLC tumors. Additionally radiotherapy should be offered in patients with N2 lymph nodes. In advanced stage IIIB/IV or inoperable NSCLC pts, a multidisciplinary treatment should be offered consisted of 4 cycles of cisplatin-based chemotherapy plus a 3rd generation cytotoxic agent or a cytostatic (anti-EGFR, anti-VEGFR) drug.

KEY WORDS Non-small cell lung cancer (NSCLC); lung cancer; treatment; targeted treatment

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Introduction

Lung Cancer was the most common cause of death from cancer with more than 1.38 million deaths worldwide (1).

Non-small cell lung cancer (NSCLC) accounts for the 80% of all lung cancers. Its main types are: adenocarcinoma (including BAC) 32-40%, squamous 25-30%, large cell 8-16%.

Till lately there were obscure guidelines for the management of NSCLC. Now there is a global attempt to tailor the management of the cancer according to the specific patient's characteristics, such as the extent of the disease and a number of prognostic and predictive factors.

The IASLC staging project (2) have shown statistical superiority on patient survival in early pathological stage and with median Overall Survival 95 mos for stage IA, 75 mos for stage IB, 44 mos for IIA, 29 mos for IIB and 19 mos for IIIA. Nevertheless a significant influence factor in OS was the subtype of tumor cells (83 mos for Bronchoalveolar carcinoma, BAC, 45 mos for Adenocarcinoma, ADCA, 44 mos for Squamous, SQUAM, 34 mos for Large cell carcinoma, LARGE and 26 mos for Adenosquamous, ADSQ) (Figure 1).

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Management of NSCLC according to the extent of the disease

Early disease stage I-IIIA

Stage IA

Once histopathological diagnosis is made, if the patients generally consider fit for radical treatment these will undergo surgical intervention. Usually lobectomy or greater resection is recommended rather than sublobar resections (wedge or segmentation). In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection because of comorbid disease or decreases in pulmonary functions segmentectomy/anatomical resection is recommended over non-surgical interventions. Further management will base on initial extent of the disease, postoperative information and on patient preference and decision.

The use of pre-operative or post-operative chemotherapy or radiation therapy in stage I NSCLC is not recommended by small randomized studies.

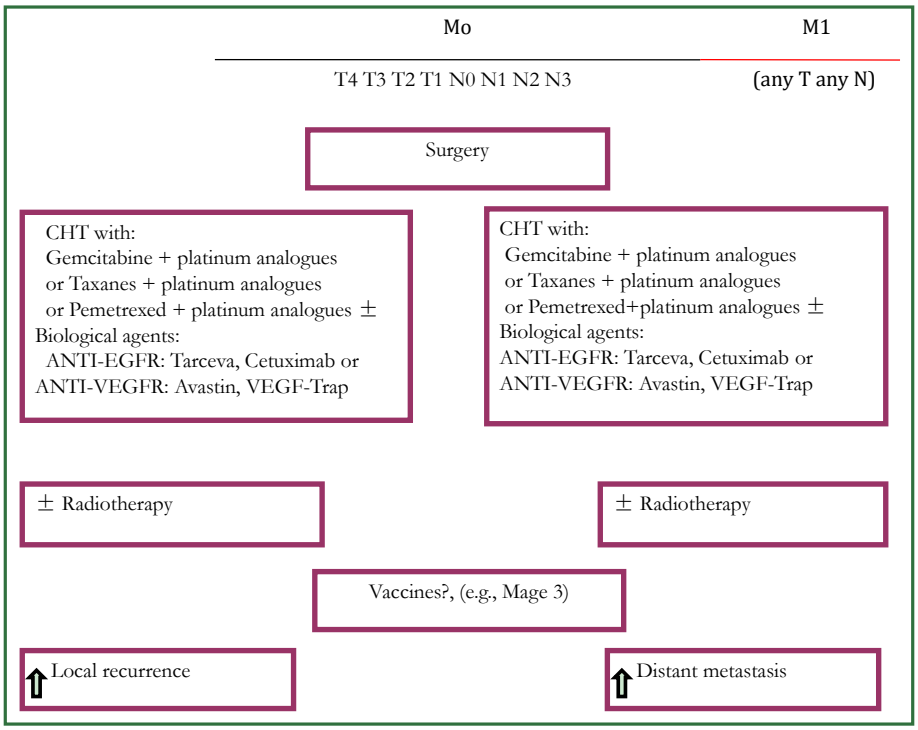

Figure 1. Treatment algorithm for NSCLC. (T, tumor; N, lymphnodes; M, metastasis).

Table 1. New adjuvant treatment.

Theory	Reality
Micrometastasis reduction	Unknown
Downstaging	50%
Patient acceptance increase	+++
Relapse rate increase	±
Morbidity/mortality increase	±
Survival increase	±

Stage IB

The meta-analysis over review gave non-clear evidence-based for adjuvant or induction treatment in stage IB patients after radical tumor resection. Only selective patients and patients that are participating in protocols are candidates for further treatment.

Stage II

Patients with stage II are usually consider for multidisciplinary treatment strategies.

The administration of postoperative radiation therapy for the improvement of survival is not recommended in patients who undergo radical resection of stage II tumor with N_1 lymph node metastasis [stage II (N_1) NSCLC].

In patients who undergo radical resection of stage II tumor and are in a good physical condition, adjuvant platinum-based chemotherapy should be offered between 4th and 8th week following the thoracotomy (adequate wood healing, non residual inflammatory or infectious complications). Patients in stage II, who are not candidates for surgical approaches due to comorbidities (e.g., pulmonary risk factors), could be considered for chemo-radiotherapy strategies.

Locally advanced IIIA and selected IIIB

Patients in stage $IIIA_1$-$IIIA_2$ (3) are usually operated with mediastinal lymphadenectomy followed by platinum-based of adjuvant chemotherapy.

Postoperative radiation therapy alone can reduce the relapse locally without increasing survival.

A multidisciplinary management of $IIIA_3$ and $IIIA_4$ patients becomes crucial. Patients with proven N_2 involvement ($IIIA_3$ and $IIIA_4$) could be treated by induction chemotherapy followed by surgery followed by platinum-based chemo radiotherapy.

Stage IIIB is typically considered for concurrent chemo radiotherapy approaches. In selected cases surgery will be incorporated within clinical trials.

Until now there is an obscure evidence of a randomized phase III pre-operative trials (Table 1).

Nevertheless a meta-analysis from five randomized trials of cisplatin-based therapy revealed a survival benefit for adjuvant chemotherapy (HR for death =0.89; 99% CI: 0.82 to 0.96; P=0.005) (4).

Table 2. Randomized clinical trials (including more than 100 pts) of platinum-based chemotherapy plus BSC *vs.* BSC in advanced NSCLC.

Authors	Cytotoxic drugs	No of pts drugs/BSC	MS (mos) drugs/BSC	P value
Rapp *et al.*/1988 (5)	CAP	198/53	5.7/3.9	0.05
Woods *et al.*/1990 (6)	Vdp		7.5/3.9	0.01
Thongprasert *et al.*/1999 (7)	IErP/MVdp	189/98	6.0/2.5	0.006
Cullen *et al.*/1999 (8)	MIP	175/175	6.7/4.8	0.03
Spiro *et al.*/2004 (9)	Cisplatin-based, MMC-Ifo-CDDP, MMC-VDS-CDDP, CDDP-VDS, CDDP-VNR	364/361	8/5.7	0.01

Table 3. Results of six new agents in advanced NSCLC as monotherapy and in combination with platinum analogues (Pt) (10).

Agent	Complete response + Partial response	Complete response + Partial response combination with (Pt) analogues
Vinorelbine	>15%	30-45% (C)
Gemcitabine	>15%	28-54% (C)
Paclitaxel	>15%	27-44% (C)
Docetaxel	>15%	25-62% (C)
Docetaxel	>15%	26-51% (Cb)
Irinotecan	>15%	50% (C)
Pemetrexed	<15%	30.6% (C)

Table 4. Phase I/II studies of taxanes plus carboplatines in advanced NSCLC.

Study	References	Paclitaxel (P) Docetaxel (D)	Carboplatin	Patients (n)	Objective response	Median survival wk	Patients alive at 1 year %
Langer	(11)	175-280 mg/m^2 (P)	7,5	22	12 (55%)	54	56%
Langer	(12)	135-215 mg/m^2 (P)	7,5	35	9 (26%)	NR	NR
Bunn	(13)	135-250 mg/m^2 (P)	300-400 mg/m^2	50	13 (26%)	29	28%
Natale	(14)	150-250 mg/m^2 (P)	6	42	26 (62%)	NR	NR
Rowinsky	(15)	175-250 mg/m^2 (P)	7-9	19	7 (37%)	NR	NR
DeVore	(16)	200 mg/m^2 (P)	6	63	16 (25%)	32	NR
Creaven	(17)	175-250 mg/m^2 (P)	4,5	23	4 (17%)	NR	NR
Roychowdhury	(18)	225 mg/m^2 (P)	6 (day 2)	7	4 (57%)	NR	NR
Greco	(19)	225 mg/m^2 (P)	6	100	38 (38%)	35	42%
Camp	(20)	175 mg/m^2 (P)	9,11	100	38 (38%)	53	50%
Conner	(21)	135 mg/m^2 (P)	4	15	2 (3%)	NR	NR
Zarogoulidis *et al.*	(22)	100 mg/m^2 (D)	6	94	46 (54.7%)	53	32%

Management of advanced non-small cell lung cancer stage IIIB-IV

Patients of stage IIIB-IV should understand that the treatment goals are the prolongation of life, the palliation of symptoms and the improvement of QoL.

Chemotherapy vs. best supportive care (BSC)

A number of randomized studies compared the overall survival of NSCLC patients in stage IIIB and IV between chemotherapy and BSC and they revealed a real advantage for chemotherapy treatment (Table 2).

Cytotoxic agents active against NSCLC are platinum analogues (cisplatin-carboplatin), ifosfamide, mytomycin C, vindesine, vinblastine, etoposide, gemcitabine, paclitaxel, docetaxel, vinorelbine, pemetrexed.

In the guidelines of ACCP, ASCO, FNCLCC and the Ontario Program, chemotherapy of advanced stage IIIB/IV pts, should be platinum-based with a new (3rd generation) single-agent. In Table 3 is presented the response in 3rd generation cytotoxic drugs as monotherapy and in combination with platinum analogues (10). In Tables 4-6 are presented the results from Phase I/III studies of 3rd generation cytotoxic agents in combination with older

Table 5. Phase III trials of multidrug combinations incorporating newer agents in the treatment of advance NSCLC.

New agent	First author	Patients (n)	Chemotherapy regimens	Response rates (%)	Median survival weeks
Vinorelbine	Le Chevalier *et al*., 2001 (23)	412	Vinorelbine	14	36
			Vinorelbine, cisplatin	30*	43*
	Depierre (24)	231	Vinorelbine	16	32
			Vinorelbine, cisplatin	43*	33
	Baldini *et al*., 1998 (25)	140	Vinorelbine, carboplatin	14	34
			Vinorelbine, cisplatin, ifosfamide	17	38
			Cisplatin, vindesine, mitomycin	14	36
	Wozniak (26)	432	Cisplatin	12	26
			Vinorelbine, cisplatin	26	35
	Frasci (27)	120	Vinorelbine	15	18
			Vinorelbine, gemcitabine	22	29
Paclitaxel/ Docetaxel	Kelly *et al*., 2001 (28)	406	Vinorelbine, cisplatin	28	32
			Paclitaxel, carboplatin	24	34
	Giaccone (29)	332	Paclitaxel 175, cisplatin	44	41
			Cisplatin, teniposite	30	42
	Gatzemeier (30)	414	Cisplatin 100	17	37
			Paclitaxel 175, cisplatin 80	26*	35
	Bonomi (31)	599	Paclitaxel 250, cisplatin	28*	44*
			Paclitaxel 135, cisplatin	25*	41*
			Cisplatin, etoposide	12	33
	Schiller *et al*., 2002 (32)	1,207	Cisplatin, paclitaxel	21	32
			Cisplatin, gemcitabine	22	30
			Cisplatin, docetaxel	17	32
			Carboplatin, paclitaxel	17	32
	Georgoulias *et al*. (33)	302	Docetaxel, cisplatin	36*	52
			Docetaxel	18	40
	Stathopoulos *et al*. (34)	360	Paclitaxel, vinorelbine	46	44
			Paclitaxel, carboplatin	43	40
Gemcitabine	Crino (35)	307	Gemcitabine, cisplatin	38*	37
			Cisplatin, mitomycin, ifosfamide (MIC)	26	42
	Cardenal (36)	135	Gemcitabine, cisplatin	41*	38*
			Cisplatin, etoposide	22	31
	Sander (37)	522	Cisplatin	11	33
			Gemcitabine, cisplatin	30*	38
	Comella *et al*. (38)	180	Gemcitabine, cisplain, vinorelbine	47*	51*
			Gemcitabine, cisplatin	30	42*
			Cisplatin, vinorelbine	25	35
Irinotecan (CPT-11)	Masuda (39)	398	Cisplatin 80, irinotecan 60	43	50
			Cisplatin 80, vindesine	31	47
			Irinotecan 100	21	46
	Negoro (40)	398	Irinotecan, cisplatin	44	50
			Cisplatin, vindesine	32	46
			Irinotecan	21	46
Pemetrexed	Scaglioti *et al*. (41)	1,725	Cisplatin, pemetrexed	31	40
			Cisplatin, gemcitabine	28	40

NR, not reported; NS, not significant; *, P<0.05.

Table 6. Response rate and survival with doublet *vs.* single-agent regimens and triplet *vs.* doublet regimens (10).

	No. of comparisons	No. of patients	Treatment effect P value
Response rate			
2 *vs.* 1 agents	33	7,175	<0.001
3 *vs.* 2 agents	35	4,814	<0.001
1-year survival			
2 *vs.* 1 agents	13	4,125	<0.001
3 *vs.* 2 agents	10	2,249	0.88
Median survival			
2 *vs.* 1 agents	30	6,022	<0.001
3 *vs.* 2 agents	30	4,550	0.97

Table 7. Phase I/II studies of non-platinum doublets in advanced NSCLC (10).

Regimen	Studies (n)	Assessable patients (n)	RR (%) range	AR	MS (months)	IYS (%)
Gem/VNR	6	286	19-73	41	9,12	NR
Doc/VNR	6	174	20-88	48	5,9	24
Pac/Gem	3	117	30-35	33	NR	NR
Doc/Gem	2	73	38-39		13	51
Doc/CPT-11	1	32	34		9,8	38
Pac/VNR	1	25	16		NR	NR
Gem/Topotecan	1	13	30		NR	NR

agents. Non-platinum containing chemotherapy may be used as an alternative to platinum-based regimen (Table 7).

Number of chemotherapy

Two randomized trials suggest that the survival benefit that pts receive from chemotherapy occurs in the first three to four cycles. Prolonged therapy may increase cumulative toxicities with insignificant increase in survival rates (42).

Concurrent vs. sequential chemo radiotherapy

Several phase III randomized trials of concurrent *vs.* sequential chemo-radiotherapy have revealed: (I) improved median survival time (average of 15.7 *vs.* 14 months) (43); (II) improved 2-year survival rates (35% *vs.* 23%) (44); (III) improved 5-year survival (15.8% *vs.* 8.9%, P=0.039) (45). On the other hand, an increased toxicity with an acute esophagitis incidence of 26% was observed in the concurrent arm (43).

Baggstrom *et al.*, have performed a meta-analysis of the published literature comparing platinum-based regimens including a third-generation agent to older standard platinum-based regimens. The new third-generation regimens increased patient survival compared to the older regimens (RR, 1.14; 95% CI: 1.01 to 1.29). There was an absolute increase in the 1-year survival rate of 4% using the newer combination regimens compared to the older regimens (P=0.04) (46).

Treatment according to prognostic and predictive factors

Excision repair cross-complementation group 1 and regulatory subunit of ribonucleotide reductase (ERCC1, RRM1)

A number of studies have shown the importance of RRM1 and ERCC1 expressions (47,48) in tumor cells. High RRM1 and ERCC1 expression is associated with longer survival after resection of early stage NSCLC (prognostic). Additionally high RRM1 and ERCC1 expression are predictors of lower tumor response rate and shorter survival for treatment with gemcitabine and cisplatin (predictive). Finally low ERCC1 expression is associated with survival benefit from adjuvant chemotherapy for NSCLC (predictive). These biomarkers have not been prospectively validated.

Thymidylate synthase expression (TS)

Baseline expression of the TS gene and protein were significantly higher in squamous cell carcinoma when compared with adenocarcinoma (49). Preclinical data indicate that high

expression of TS correlates with reduced sensitivity to cytotoxic agent pemetrexed (antifolate) (50). In JMDB study 1,700 primary untreated NSCLC pts of stage IIIB/IV and PS 0-1 were randomized either to cisplatin plus gemcitabine or ciplatin plus pemetrexed given every three weeks up to six cycles. Overall Survival found to be similar for both treatment arms (Median 10.3 mos; HR 0.94; 95%, CI: 0.84-1.05). Nevertheless, analysis of pts by histology showed a statistical significant better OS of non-squamous histology pts in cisplatin + pemetrexed arm compared to cisplatin + gemcitabine arm (11 *vs.* 10.1 mos) and this difference for those with adenocarcinoma was improved in the pemetrexed arm by 12.6 *vs.* 10.9 mos respectively (P=0.08). The results of JMDB study indicating a predictive role of tumor histology and cisplatin/pemetrexed has been registered in first line standard therapy in non-squamous NSCLC pts (41).

Biological agents

Progress in understanding cancer biology and mechanisms of oncogenesis has allowed the development of treatment against specific molecular targets, such as epidermal growth-factor receptor (EGFR) and vascular endothelial growth factor (VEGF), which are of special interest in NSCLC.

The most frequently targeted pathways in NSCLC have involved the EGFR and the Vascular Endothelial Growth Factor and its Receptor (VEGF, VEGFR).

The EGFR is a member of ErbB family of transmembrane receptors Tyrosine Kinases (TKs) and plays a major role in the malignant cell phenotype.

The role of EGFR inhibitors in the first line setting as single agents was explored after the failure to show benefit in combination with chemotherapy. In the IPASS trial (51), 1,217 chemo naïve, East Asian with adenocarcinoma histology, never or light smokers pts randomized to receive the EGFR inhibitor gefitinib (G) or carboplatin plus placlitaxel (CP). The trial demonstrating superior PFS in the gefitinib arm compared with CP (HR 0.74; 95%, CI: 0.65-0.85; P<0.0001) and Overall Response Rate (43% *vs.* 32.2%; P=0.0001) but similar Overall Survival (median mos 18.6 *vs.* 17.3). Patients with EGFR mutations had the most benefit from gefitinib, with a 51% reduction in progression (HR 0.48; P<0.0001) whereas those pts without EGFR mutation, responded better to chemotherapy (P<0.0001).

Erlotinib inhibits the tyrosine kinase activity of EGFR and has been studied extensively in randomized Phase III trials, yielding promising results, especially as second-line, third line, and maintenance therapy, and in patients with activating mutations of the EGFR receptor.

In the EURTAC multicentre, randomized phase III trial (52), 174 non-squamous EGFR mutant patients received platinum-based chemotherapy or Erlotinib. Median PFS was 9.7 mos in the erlotinib group compared with 5.2 mos in the chemotherapy group (P<0.0001).

Angiogenesis place a critical role in tumor development. Anti-angiogenic therapy such as the use of TKIs that block the VEGFR, aims to disrupt existing capillaries that feed a tumor and prevent new vessels from forming around it.

In two randomized phase III studies the ECOG 4599 (Eastern Cooperative Oncology Group) (53) and AVAiL (AVAstin in Lung) (54) the adding of anti-angiogenetic agent bevacizumab to paclitaxel/carboplatin in the first and to gemcitabine/cisplatin in the 2nd study, indicated improved of efficacy and PFS [(6.2 *vs.* 4.5 mos, P<0.0001) and (P=0.003 for a dose of bevacizumab of 7.5 mg/kg or P=0.03 for a dose of bevacizumab of 15 mg/kg respectively)].

All the including in the two above studies pts were chemotherapy naïve ECOG PS of O or 1 with newly diagnosed stage IIIB/IV and non-squamous NSCLC confirmation.

In the ECOG 4599 study there was a statistical significant improvement even in OS in the arm receiving bevacizumab compared to the control arm (HR 0.79; 95%, CI: 0.67-0.92; P=0.003). Based on the results of ECOG 4599 and AVAiL, the use of bevacizumab is recommended in combination with chemotherapy in non-squamous cell carcinoma (limitations, clinical significant hemoptysis, as controlled, hypertension, therapeutic anticoagulation).

More recently, the BeTa (Bevacizumab/Tarceva) trial (55), investigating the benefits of addition of bevacizumab to erlotinib for second-line treatment of advanced NSCLC, showed a doubling of progression-free survival with combination therapy (3.4 months) as compared with erlotinib monotherapy (1.7 months, P=0.001) but no benefit in terms of overall survival.

In another randomized trial (56), each targeted therapy alone (bevacizumab, erlotinib) compared with their combination and cytotoxic platinum-based chemotherapy alone in previously untreated and advanced non-squamous NSCLC, following by administration of these agents as maintenance therapy.

This randomized study suggests that bevacizumab enhances the activity of chemotherapy but this did not translate into longer overall survival.

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