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Recent Achievements in Lung Adenocarcinoma

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INTRODUCTION

Lung Cancer is one of most common malignancies and the leading cause of cancer deaths worldwide, and 80%~85% cases are the Non-small cell lung cancers **(NSCLC)**. Lung adenocarcinoma **(LAC)** is the most common histologic subtype of NSCLC, accounting for more than 50%, besides, the incidence rate is increasing. A widely divergent clinical, radiologic, molecular, and pathologic spectrum exists within LAC [1,2]. Most adenocarcinomas arise in the peripheral, parenchymal part of the lung. These tumors show a wide range in size, and may be multifocal. LAC is more prone to hematogenous spread, such as brain, bone and Intrapulmonary metastasis. Moreover, it often has unique genes related to susceptibility and good response to treatment with specific agents.

RISK FACTORS

The primary risk factor for LAC is smoking tobacco, which accounts for most lung cancer-related deaths [3]. Concerning carcinogenesis in never smokers, environmental tobacco smoke **(ETS)** at home, work and other places have been supposed to be the cause of LAC in never smokers [4]. Besides ETS, reported carcinogens include radon, cooking oil vapor, indoor coal burning, hormonal factors (after hormonal replacement therapy), occupational chemical exposure including asbestos/heavy metals, infectious factors, and air pollution [5].

PATHOLOGY

In 2015, the classification for LAC was revised by an international panel (IASLC/ATS/ERS), which has been adopted by the WHO [6]. The revised classification recommends immuno-histochemically **(IHC)** and molecular studies.

The categories for adenocarcinoma include:

1) Atypical adenomatous hyperplasia **(AAH)**, which is a preinvasive lesion: usually ≤0.5 cm.
2) Adenocarcinoma in situ **(AIS)**, which is a preinvasive lesion: usually ≤2 cm nodule, occasionally reach 3cm, including mucinous, nonmucinous.
3) Minimally invasive adenocarcinoma **(MIA)**: ≤3 cm nodule with ≤5 mm of invasion, including mucinous, non-mucinous.
4) Invasive adenocarcinoma, predominant growth pattern: lepidic >5 mm of invasion, including lepidic growth, acinar, papillary, micropapillary, or solid with mucin. Micropapillary pattern correlates with poor prognosis.
5) Variants of invasive adenocarcinoma (includes formerly mucinous BAC): including mucinous adenocarcinoma, colloid, fetal, and enteric morphologies. Micropapillary correlates with poor prognosis. Mucinous adenocarcinoma pattern correlates with poor prognosis.

IHC is necessary in LAC diagnoses, and the panel of TTF-1 and Napsin A are utmost important. TTF-1 immunoreactivity is seen in primary pulmonary adenocarcinoma in the majority (70%–100%) of non-mucinous adenocarcinoma subtypes [7]. Napsin A is an aspartic proteinase expressed in normal type II pneumocytes and in proximal and distal renal tubules-appears to be expressed in >80% of LAC and may be a useful adjunct to TTF-1 [8].

Molecular testing is very important for LAC treatment. The international panel and NCCN recommend that all patients with adenocarcinoma be tested for EGFR mutations, anaplastic lymphoma kinase **(ALK)** gene rearrangements, ROS1 rearrangements, and programmed death **(PD-1)** receptor expression levels in tumor tissues. Other rare driver gene mutations detection such as BRAF V600E mutations, RET gene rearrangements, high-level MET amplification or MET exon 14 skipping mutation, and HER2 are also advised [9]. The newly established targeted next-

generation sequencing **(NGS)** provides a promising method for diagnostic purposes by enabling the simultaneous detection of multiple mutations in various genes in a single test [10]. While, blood in particular serum, is a good substitute when tumor tissue is absent or insufficient for molecular testing [11].

TREATMENT

Surgery, RT and systemic therapy are the 3 modalities most commonly used to treat patients with NSCLC. They can be used either alone or in combination depending on the disease status. A new edition of the AJCC Cancer Staging Manual (8th edition) was published in late 2016 [12]. With the AJCC staging, locally advanced disease is stage III; advanced disease is stage IV.

Management of Early Stage LAC

Surgical resection of the lung remains the best treatment for patients with lung cancer whose extension is limited to the primary lesion or to the hilar lymph nodes, provided that the patient has good functional reserve. These patients belong to stage IA, IB, IIA and IIB [13].

The efficacy of modern conventional radiotherapy in patients with early-stage NSCLC is modest and most of the patients experience local relapse after treatment. Most of the series exploring radical radiotherapy in early-stage NSCLC reported outcomes of those patients who were inoperable due to comorbidities or did not wish to undergo surgery [14,15]. SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function) [16-18].

Management of Locally Advanced LAC

The standard of care for patients with inoperable stage II (node positive) and stage III is concurrent chemotherapy/RT [19-21]. Since the stage IIIA **(N2)** is very heterogeneous, surgery for patients with stage IIIA disease is sometimes controversial. Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy) and is recommended for resectable superior sulcus tumors.

Management of Advanced LAC

Chemotherapy

Chemotherapy is one of the most important therapies of lung adenocarcinoma. For advanced lung adenocarcinoma, Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care. For many years, the treatment of patients with metastasis was informed most by Eastern Cooperative Oncology Group **(ECOG)** 1594, which asked the question of whether any specific platinum doublet was superior to a reference regimen of cisplatin and paclitaxel [22]. A total of 1207 patients with NSCLC

were randomized to receive one of four regimens: (1) cisplatin and paclitaxel, (2) cisplatin and gemcitabine, (3) cisplatin and docetaxel, or (4) carboplatin and paclitaxel. The overall response rate of 19% and median overall survival **(OS)** of 7.9 months were not significantly different in any of the four arms. There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with adenocarcinoma histology, in comparison to cisplatin/gemcitabine.

However, more recent studies have shown the further refining NSCLC by histologic subtype is critical to optimal management. The notable JMDB, JMEI, JMEN and PARAMOUNT studies showed that there is superier efficacy and reduced toxicity for cisplatin/pemetrexed ih the first/second -line and maintenance therapy of patients with adenocarcinoma histology, in comparison to other agents. In the first therapy, JMDB study showed that overall survival was statistically superior for cisplatin/ pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n=847; 12.6 v 10.9 months, respectively) [23]. In the phase III PARAMOUNT trial (86% adenocarcinoma), pemetrexed continuation maintenance therapy reduced the risk of disease progression versus placebo (hazard ratio **[HR]**, 0.62; 95% CI, 0.49 to 0.79; P<.001), pemetrexed therapy resulted in a statistically significant 22% reduction in the risk of death (HR, 0.78; 95% CI, 0.64 to 0.96; P<.0195; median OS: pemetrexed, 13.9 months; placebo, 11.0 months). Survival on pemetrexed was consistently improved for all patient subgroups, including induction response: complete/ partial responders (n=234) OS HR, 0.81; 95% CI, 0.59 to 1.11 and stable disease (n=285) OS HR, 0.76; 95% CI, 0.57 to 1.01) [24]. In JMEI study, patients with non-squamous disease, the improvement in both progression-free and overall survival was significant for pemetrexed in the adenocarcinoma, (progression-free survival HR 0•44, 95% CI 0•36–0•55; and overall survival HR 0•70, 0•56–0•88) [25]. The JMEI study was designed to compare the efficacy and toxicity of pemetrexed versus docetaxel in patients with advanced non–small-cell lung cancer **(NSCLC)** previously treated with chemotherapy [26]. Overall response rates were 9.1% and 8.8% (analysis of variance P=.105) for pemetrexed and docetaxel, respectively. Median progressionfree survival was 2.9 months for each arm, and median survival time was 8.3 versus 7.9 months (P=not significant) for pemetrexed and docetaxel, respectively.

Targeted Therapy

EGFR mutations: Discovery of epidermal growth factor receptor **(EGFR)** sensitizing mutations in 2004 changed the treatment paradigm for advanced non–small cell lung cancer **(NSCLC)**. EGFR was found over expressed on malignant cells compared with benign neighboring cells [27], Activation of EGFR on the cell was found to be associated with cell proliferation, angiogenesis, invasion, metastasis, and an ability to escape apoptosis [28]. However, not all patients responded to EGFR Tyrosine Kinase Inhibitors **(EGFR-TKIs)**. East Asians, women and never smokers with adenocarcinoma were more likely to response with EGFR-TKIs. It was found these responses were related to exon 19 deletions (del 19) and exon 21 L858R point mutation [29], while patient with del 19 seem to have a better outcome compared with those with L858R when treated with EGFR-TKIs [30-35]. These mutations are present in approximately 20%-60% of lung adenocarcinomas.

Nine randomized phase III trials have shown that EGFR-TKIs surpass standard first-line platinum chemotherapy in objective response rate, PFS, and quality-of-life measures for patients with activating EGFR mutations, but have failed to show a difference in OS [30,32,33,36-41]. Three meta-analysis suggest there was no significant differences among gefitinib, erlotinib and afatinib [42-44].

Although first-line TKIs have been proved effective in blocking an oncogenic addicted driver mutation, progression generally occurs at approximately 9 months in most patients. Escape mechanisms include newly acquired gatekeeper EGFR mutations **(T790M)**, bypass pathways (MET/HER2 [MNNG HOS Transforming gene/human epidermal growth factor receptor] amplification), activation of downstream pathways (PIK3CA [phosphatidylinositol 30-kinase], BRAF (v-raf murine sarcoma viral oncogene homolog B) mutations), and histologic transformation to small cell. While exon 20 T790M mutation response for 50%-60% of the progression on a first-generation EGFR TKI. Second-generation TKIs (afatinib, dacomitinib and neratinib) were initially developed in an attempt to overcome acquired T790M resistance that arose after treatment with first-generation TKIs. Although preclinical data against T790M mutated cell lines were encouraging, dose-limiting toxicities hindered translation of those effects clinically, resulting in poor response rates in T790M-positive patients [45-48]. In contrast, third-generation TKIs (osimertinib, rociletinib, olmutinib, ASP8273, EGF816) have selective activity against T790M. The recent approval of osimertinib has provided patients with a second-line option against T790M mutated NSCLC. For those who are T790M negative or progress on a third-generation TKI, chemotherapy is still recommended outside a clinical trial.

ALK rearrangements: Translocations involving the ALK (anaplastic lymphoma kinase) tyrosine kinase are present in approximately 2%-4% of lung adenocarcinomas in Caucasian populations, more frequently in younger patients and light or never-smokers. Patients with tumors harbouring ALK rearrangement more often present with brain and liver metastases as well as pleural and pericardial eclusions [49]. The presence of an ALK rearrangement is strongly predictive of sensitivity to ALK inhibitor therapy.

Crizotinib-an inhibitor of ALK, ROS1 and some MET tyrosine kinases (high-level MET amplification or MET exon 14 skipping mutation)-is approved by the FDA for patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements (ie, ALK-positive disease) or ROS1 rearrangements. Crizotinib yields very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements, including those with brain metastases [50]. Randomized phase III trials have compared crizotinib with standard second-line (ie, subsequent) chemotherapy (PROFILE 1007) and with standard first-line therapy (PROFILE 1014). Based on these trials, crizotinib is recommended for first-line therapy and subsequent therapy in patients with ALK-positive disease [51,52].

Several resistance mechanisms to crizotinib have been identifed, including active ALK-dominant (resistance mutations and ALK copy number gain) and ALK non-dominant pathways (the outgrowth of clones containing a separate activated oncogene) [53,54]. Second-generation ALK inhibitors are more potent against ALK *in vitro* than crizotinib and can overcome selected ALK kinase domain mutations associated with resistance to crizotinib. Among these, ceritinib and alectinib are in the late phase of their development. Both drugs demonstrate activity against central nervous system disease, owing to their related better CNS penetration. Ceritinib and alectinib have been approved in the setting of crizotinib resistance in some countries [55].

ROS1 eearrangements: Although ROS1 is a distinct receptor tyrosine kinase, ROS1 has a high degree of homology with ALK (approximately 50% within the kinase domain and 75% within the ATP-binding site) [56]. The majority of patients with ROS1-positive NSCLC respond to the first-generation ALK inhibitor crizotinib, however, certain other ALK inhibitors such as alectinib do not appear to have activity against ROS1-positive NSCLC. ROS1 rearrangements occur in 1%-2% of patients with NSCLC [57]. Similar to testing for ALK rearrangements, testing for ROS1 is also done using FISH.

Antiangiogenic agents

Bevacizumab: Tumour angiogenesis is one of the main targets in cancer treatment. As a matter of fact, the addition of bevacizumab to paclitaxel and carboplatin in first-line treatment in patients affected by nonsquamous NSCLC showed a significant survival benefit [58]. Meta-analysis from Sheng confirmed the addition of antiangiogenic agents to taxanes-containing chemotherapy was associated with a significantly longer OS and PFS in advanced NSCLC, especially for nonsquamous female [59], a significant improvement in OS when antiangiogenic agents were used in combination with docetaxel in patients who failed first-line chemotherapy [60]. In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC [61]. The ECOG recommends bevacizumab in combination with paclitaxel/ carboplatin for select patients with advanced non-squamous NSCLC based on the results of phase 2 to 3 clinical trials (ECOG 4599) [58]. Bevacizumab in combination with chemotherapy (ie, carboplatin/paclitaxel, carboplatin/pemetrexed, cisplatin/ pemetrexed) is one of the recommended options for patients with a PS 0 to 1 and non-squamous NSCLC or NSCLC NOS and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations or PD-L1 expression. Bevacizumab is not recommended for patients with squamous cell NSCLC.

Nintedanib: Nintedanib is an oral angiokinase inhibitor that targets pro-angiogenic pathways mediated by VEGFR [58-60], fibroblast growth factor receptors **(FGFR)** and platelet-derived growth factor receptors **(PDGFR)**. In LUME-Lung 1 trial [62], the combination of docetaxel and nintedanib was compared to docetaxel alone as second-line treatment in 1314 patients affected by advanced NSCLC. Primary endpoint was PFS that resulted statistically significant improvement in docetaxel plus nintedanib arm (3.4 vs. 2.7 months, HR 0.79, 95% CI 0.68-0.92, p = .0019). OS

was comparable in the two arms (10.1 vs. 9.1 months, HR 0.94, 95% CI 0.83-1.05, p = .2720) but significantly longer in patients with adenocarcinoma subtype receiving the combination of nintedanib plus docetaxel (12.6 vs. 10.3 months, HR 0.83, 95% CI 0.70-0.99, p = .0359). The randomized trial LUME-Lung 2 evaluated the addition of nintedanib to pemetrexed in 713 patients affected by advanced lung adenocarcinoma. The final analysis showed a modest but statistically significant improvement in PFS (4.4 vs. 3.6 months, HR 0.83, 95% CI 0.70-0.99, p = .04), but no difference in OS and RR was found [63]. Further studies have shown an OS benefit of nintedanib plus docetaxel as second-line therapy regardless of the first-line regimen containing taxanes [64] or pemetrexed [65]. In EU, nintedanib received approval in patients with locally advanced, recurrent or metastatic, NSCLC of adenocarcinoma histotype as second-line treatment in combination with docetaxel.

Ramucirumab: Ramucirumab is a fully human IgG1 monoclonal antibody targeting the extracellular domain of VEGFR2. A phase 3 randomized trials **(REVEL)** assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC that had progressed. Improvement in OS was statically significant in favour of the combination arm (10.5 vs. 9.1 months, HR 0.86, 95% CI 0.75-0.98, p = .023), but not clinically relevant. The forest plot of the trial suggests a benefit of ramucirumab on OS in patients with nonsquamous (11.1 vs. 9.7 months, HR 0.83, 95% CI 0.71-0.97) [66]. Ramucirumab is currently approved in combination with docetaxel for platinum-resistant metastatic NSCLC from FDA but not from EMA.

Immunotherapy

Immunotherapy is a new paradigm for the treatment of NSCLC, and targeting the PD-1 pathway is a promising therapeutic option. The PD-1 receptor is an immune checkpoint inhibitor expressed on activated B and T cells that normally down-modulates excessive immune response. Binding of PD-1 to its ligands (PD-L1 and PD-L2) on tumor cells suppresses T cells through a negative feedback loop, leading to evasion of the immune response. Therefore, inhibition of PD-1 pathway is a novel therapeutic approach for treating cancer.

Nivolumab: Nivolumab is a fully humanized IgG4 antibody against PD-1. In Checkmate 057, 582 patients with stage IIIB/IV nonsquamous NSCLC who progressed during or after a first-line platinum-based chemotherapy were randomly assigned to receive nivolumab or docetaxel [67]. Median OS was 12.2 months in nivolumab group and 9.4 months in docetaxel group (HR 0.73, 95% CI 0.59-.089, p = .002); survival rate at 1 year was 51 and 39 %, at 18 months was 39 and 23 %, respectively. Subgroup analysis for OS showed a significant benefit of nivolumab for KRAS mutated patients (HR 0.52, 0.29-0.95), no advantage from nivolumab treatment was seen in EGFR mutated patients (HR 1.18, 0.69-2.00), in never-smokers (HR 1.02, 0.64-1.61) and in third-line therapy (HR 1.34, 0.73-2.43). In CheckMate 017 and Checkmate 057, levels of expression of PD-L1 were not prognostic nor predictive of response to treatment.

The NCCN Panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic non-squamous NSCLC who have progressed on or after first-line chemotherapy based on data from a phase 3 randomized trial (CheckMate-057) and FDA approval.

Pembrolizumab: Pembrolizumab is a fully humanized IgG4 antibody against PD-1. KEYNOTE-001 is a phase I trial assessing safety and efficacy of Pembrolizumab in 495 patients with advanced NSCLC [68]. In the study population, most of patients had a nonsquamous NSCLC (81%). The ORR was 19.4 % with a median duration of response of 12.5 months and resulted independent from dose, schedule and histologicanalysis, but it was superior in current or former smokers if compared with never-smokers (22.5 vs. 10.3 %). KEYNOTE-010, a phase II/III trial, compared pembrolizumab (at a dosage of 2 or 10 mg/kg) to docetaxel in previously treated patients affected by NSCLC [69]. OS was longer either for pembrolizumab 2 mg/kg (HR 0.71, 95% CI 0.58-0.88, p=.0008) and for pembrolizumab 10 mg/kg versus docetaxel (HR 0.61, 95% CI 0.49-0.75, p=.0001). PFS did not reach any statistical significance (3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel). Among patients with at least 50 % of tumour cells expressing PD-L1, OS and PFS were significantly longer in pembrolizumab group, independently on dosage, than in docetaxel arm. In open-label phase 3 trial KEYNOTE-024 [70], 305 patients who had previouslyuntreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and nosensitizing mutation of the EGFR or translocation of ALKwere randomized into two groups to receive either pembrolizumab or the investigator's choice of platinum-based chemotherapy.Progression-free survival was significantly longer inthe pembrolizumab group than in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68;P<0.001, in nonsquamous subgroup, HR for disease progression or death, 0.55; 95% CI 0.39-0.76). Overallsurvival was significantly longer in the pembrolizumab group than in the chemotherapy group(hazard ratio for death, 0.60; 95% CI, 0.41 to0.89; P=0.005).In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.

Pembrolizumab was approved by the FDA in October 2015 for patients with previously treated advanced NSCLC and tumor positive for PD-L1 expression. Based on the KEYNOTE-024, The FDA granted approval to pembrolizumab for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death ligand-1 as determined by an FDA-approved test. This indication applies to patients with no EGFR or ALK genomic tumor aberrations, with high programmed death ligand-1 **(PD-L1)** expression (tumor proportion score 50%) and who have not received prior systemic chemotherapy for metastatic NSCLC.

Atezolizumab: Atezolizumab is an engineered, humanised IgG1 monoclonal antibody anti-PD-L1. The POPLAR trial was a phase 2 study comparing atezolizumab with docetaxel in 287 patients with previously treated advanced stage NSCLC [71]. The primary end point was median OS. atezolizumab was associated with a significant improvement in median OS compared with

docetaxel (12.6 months vs 9.7 months; HR, 0.73; 95% CI, 0.53-0.99; P 5 .04). The increased median OS improvement from atezolizumab compared with docetaxel was directly related to the PD-L1 expression. In the study population, most of patients had a nonsquamous NSCLC (66 %). In patients with nonsquamous disease, atezolizumab showed a benefit compared to docetaxel with a median OS of 15•5 vs. 10•9 months (HR 0.69, 95% CI 0.47-1.01). PFS was similar between atezolizumab (2•7 months) and docetaxel arm (3•0 months) (HR 0•94, 95%CI 0•72-1•23).

Recently, FDA granted a priority review to atezolizumab for the treatment of NSCLC patients who express PD-L1 and have progressed after a platinum containing regimen.

Controversy: The advancements in immunotherapy have provided a new approach for the management of patients with NSCLC, but some issues have to be still resolved. First of all, a clear cut-off value for PD-L1 positivity has not been identified and this does not allow its use as predictive marker for treatment. Secondly, the expression of PD-L1 is a dynamic process as it has been observed during treatment both with TKIs in EGFR mutated patients and with ALK inhibitors in ALK-positive NSCLC, PD-L1 expression is not a fixed but a plastic phenomenon under the pressure of tumour therapy. Thirdly, the possibility of heterogeneous expression of PD-L1 in the same patient, between locoregional disease and distant metastases, has been suggested. Finally, these agents do not follow the pattern of response expected from conventional chemotherapy, in order to establish the response criteria for immunotherapy, some investigators have proposed different criteria of response assessment called immune-related response criteria [72], but the radiologic evolution of immune response has still to be completely elucidated.

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