FEATURE

Non-small cell lung cancer:

Two decades of progress

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ABSTRACT

This review traces advances in the screening, diagnosis and staging of non-small cell lung cancer (NSCLC) and undertakes a thorough review of treatment developments over the past 20 years. It considers changes in surgical practice from open thoracotomy to video-assisted thoracoscopic lobectomy, the potential of expanding radiotherapy as definitive treatment and the evolution of thinking around sequential versus concurrent chemotherapy and radiotherapy in the advanced setting. Progress in the number and effectiveness of chemotherapies for first-line, second-line and maintenance therapy is presented. A number of agents targeting identifiable mutations have already been approved, with additional agents being investigated to overcome resistance. Current and future efforts will continue the search for actionable mutations and agents to target them. Finally, the current knowledge of and future prospects for immunotherapy, including results with the first checkpoint inhibitor, are described.

Keywords: Non-small cell lung cancer, local therapy for NSCLC, systemic therapy for NSCLC, maintenance therapy for NSCLC, targeted therapy for NSCLC, immunotherapy for NSCLC.

INTRODUCTION

Lung cancer represents a common and highly fatal diagnosis. In 2014 in Canada, lung cancer was the most commonly diagnosed cancer, with 26,100 Canadians newly affected, and caused more deaths than breast, colorectal and prostate cancers combined.[1]

Staging and histologic classification systems of non-small cell lung cancer (NSCLC) have evolved with time. The 7th edition of the TNM lung cancer staging system published in 2010[2] brought forth changes to better align the stage of disease with prognosis and treatment, including reclassification of malignant pleural effusion to M1 disease. The 2013 multidisciplinary International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASCL/ATS/ERS) classification system of lung adenocarcinoma[3] better reflects advances in prognosis and management. The new classifications of adenocarcinoma in situ and minimally invasive adenocarcinoma represent a group of patients who may achieve almost 100% disease-free survival (DFS). Great emphasis was also placed on determining the specific histology of NSCLC to align with differences in outcomes seen with specific systemic therapies.[4] Upon diagnosis, it is of upmost importance to determine the specific histologic subtype, as well as test for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations, as these results will influence management.

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With the advent of improved techniques in local therapy and new systemic therapies, as well as a move toward more personalized medicine, the outcomes and survival of patients with lung cancer is better than ever. Yet, as we look to the future, there clearly remains significant room for improvement.

SCREENING, DIAGNOSIS AND STAGING

Screening

Until the National Lung Screening Trial (NLST) was published in 2011, screening for lung cancer was not deemed to be beneficial.[5] The NLST enrolled over 50,000 patients who were considered to be at high risk: ages 55 to 74, at least a 30 pack-year history of smoking and, if they were former smokers, having quit within the last 15 years. Patients were randomized to receive either a low-dose computerized tomography (CT) scan of the thorax or a chest x-ray on an annual basis for 3 years. The low-dose CT cohort had a 20% relative reduction in lung-cancer-specific mortality, and a 6.7% reduction in overall mortality. Of concern, 96.4% of the positive results were false positives. To counter this, a predictive tool was created and validated by researchers in the Pan-Canadian Early Detection of Lung Cancer Study.[6] Using this model, the probability of malignancy within a nodule detected on screening CT could be determined with greater than 90% accuracy. While there are no active screening programs currently available in Canada, this landscape is set to change in the coming years.

Staging

CT scans are routinely performed when lung cancer is suspected, though sensitivity for detecting metastases and lymph node involvement is suboptimal.[7] As such, positron emission tomography (PET) scans have become increasingly important in the diagnosis and staging of lung cancer and

are recommended for staging of all patients with clinical stage Ib and above.[8] They are superior to CT scans for non-invasive staging of the mediastinum, and may also detect occult metastatic disease, leading to avoidance of inappropriate surgery.[9]

Accurate mediastinal staging with tissue sampling to confirm radiographic findings is required prior to forming a management plan. Mediastinoscopy has been regarded as the gold standard, with a sensitivity of approximately 80%; however, endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) have now come into widespread use as a less invasive approach. In multiple trials, the sensitivity of EUS or EBUS used alone has proven essentially equivalent to mediastinoscopy,[10] but the combination of EUS and EBUS provides significantly improved sensitivity.[11]

EARLY-STAGE NSCLC — LOCAL THERAPY

Surgery

In early-stage NSCLC, surgical resection is generally the treatment of choice. Stages I and II NSCLC are amenable to resection, which must achieve R0 results. Lobectomy was established as the gold standard surgical approach in T1N0 disease based on the only prospective, randomized data in this setting.[12] However, the extent of resection necessary remains somewhat controversial, and a prospective trial is currently being conducted (CALGB 140503) to further explore the role of sublobar resection. Until these data are available, retrospective analyses have demonstrated equivalent regional recurrence and mortality for segmentectomy compared to lobectomy, and it is thus now regarded as a safe and effective alternative to lobectomy in high-risk patients.[13] Video-assisted thoracoscopic surgical (VATS) lobectomy, a less invasive approach to resection, is associated with lower morbidity and shorter recovery time than open thoracotomy,[14] and represents a feasible alternative, particularly in higher-risk patients.

Definitive radiotherapy

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT) has emerged as the standard of care for patients with stage I disease who are medically inoperable or prefer not to undergo surgery. Prior to the advent of SABR, these patients received conventionally fractionated radiotherapy, which was associated with suboptimal local recurrence rates and median survival of 18 to 33 months.[15] In 2005, the first study examining SABR for definitive treatment of early-stage NSCLC was published,[16] and showed excellent local control rates when higher doses were employed. RTOG 0236, a prospective trial examining SABR for peripheral non-small cell lung tumours <5 cm evaluated 55 patients, in which only 1 had primary tumour failure. The estimated 3-year primary tumour local control rate was 97.6%, the locoregional control rate was 87.2%, and the overall survival (OS) rate was 55.8%.[17] At this juncture, it is unclear whether SABR should be used in patients who are medically operable as well. Accrual to trials randomizing to 2 such different treatment modalities has been difficult, leading to their premature closure (ROSEL, STARS, ACOSOG Z4099). Therefore, until further data are available, SABR should be considered an effective and safe modality for the treatment of stage I lung cancer in medically inoperable patients.

Postoperative radiotherapy

The role of postoperative radiotherapy (PORT) remains unclear. A Cochrane meta-analysis from 2000, updated in 2005, examined older methods of adjuvant radiotherapy in 10 trials comprising over 2000 individuals.[18] This revealed an 18% relative increase in death for patients who received PORT, corresponding to a 6% absolute reduction in OS. These adverse results were apparent in patients with N0 and N1 disease, but not in those with N2 disease. Later retrospective analyses revisited this question in a more modern treatment era. A review of the National Cancer Database in 2015 showed that in patients with N2 disease, PORT conferred an additional absolute OS advantage at 5 years of 4.5%.[19] As a result, many centres now offer adjuvant radiotherapy to patients with resected stage 3 (N2) NSCLC.

EARLY-STAGE NSCLC — SYSTEMIC THERAPY

The majority of recurrences after surgical resection occur systemically,[20,21] and adjuvant systemic therapy plays an important role in reducing this risk. The significance of adjuvant chemotherapy began to come to light after the NSCLC Collaborative Group's 1995 meta-analysis demonstrated a 5% absolute benefit in OS at 5 years in patients who received cisplatin-based regimens.[22] Following this, a number of randomized trials evaluated the role of adjuvant platinum-based chemotherapy.[23-28] In 2008, the LACE meta-analysis analyzed individual patient data from the 5 largest trials of cisplatin-based adjuvant chemotherapy, reporting a 5-year OS absolute benefit of 5.4%.[29] However, the value of adjuvant chemotherapy appears to differ by stage. In the LACE meta-analysis, there was a clear benefit for stage II and III disease, with HRs for death of 0.83 (0.73–0.95) and 0.83 (0.72–0.94), respectively. However, for stage IB disease, the HR was 0.93 (0.78–1.10), and in stage IA disease, there was a trend towards a detrimental outcome with the use of adjuvant chemotherapy (HR 1.40 [0.95–2.06]). CALGB 9633 specifically examined the role of adjuvant chemotherapy in patients with stage IB NSCLC by comparing adjuvant carboplatin and paclitaxel to no adjuvant chemotherapy. Overall, there was no survival benefit with adjuvant chemotherapy, though an exploratory analysis demonstrated an improvement in survival for patients with tumours ≥4 cm. In line with these findings, adjuvant chemotherapy with cisplatin and vinorelbine is considered the gold standard therapy for stages II and III NSCLC.

Targeted therapy

Interest in the use of molecular targeted therapy in the adjuvant setting has intensified, however at this time it should not be used outside a clinical trial. In NCIC BR.19, patients with stage I to III unselected NSCLC received gefitinib or placebo for 2 years in the adjuvant setting.[30] The gefitinib

group saw no benefit in OS or DFS, and there was even a trend towards worse OS (HR 3.16, p=0.15) in an exploratory analysis restricted to patients with EGFR mutation. The recently presented RADIANT randomized, placebo-controlled trial of adjuvant erlotinib in resected stage IB to III NSCLC showed a trend towards improved DFS in patients with an EGFR mutation.[31] The MAGRIT trial,[32] the largest randomized trial in NSCLC to date, was recently presented, with disappointing results. MAGE A3, a protein present on 35% of NSCLC cells, was targeted with a vaccine in the adjuvant setting. There was no difference in DFS between those who did and did not receive the vaccine.

LOCALLY ADVANCED NSCLC

Stage III disease represents a heterogeneous population. Generally, stage III NSCLC is considered inoperable and thus radiation and chemotherapy are the mainstays of treatment. Radiation was first shown to be superior to supportive care in patients with locally advanced NSCLC in 1968[33] and 20 years later the optimal dose was identified as 60 Gy delivered in 2-Gy fractions.[34] Doses in the 60–66 Gy range remain standard treatment. Recently, RTOG 0617 compared standard- versus high-dose (74 Gy) conformal radiotherapy[35] and found that the higher dose was associated with inferior survival and increased toxicity, and should therefore not be used.

The use of chemotherapy provided sequentially or concurrently with radiation improves OS compared to radiation alone, which was initially shown in early trials of induction chemotherapy with cisplatin and vinblastine prior to radiation.[36] Following this, a series of phase III trials comparing sequential to concurrent chemoradiotherapy found concurrent administration to be superior, and it became the standard of care.[37-39] Most recently, a 2010 meta-analysis looking at individual patient data from 6 separate trials reported a survival benefit with the use of concurrent rather than sequential chemoradiotherapy, with an absolute survival benefit of 5.7% at 3 years and 4.5% at 5 years.[40] Interestingly, this benefit appeared to be due to a decrease in locoregional recurrence, as there was no difference in the rate of distant progression.

There does not appear to be a benefit to adding consolidation or induction chemotherapy to concurrent chemoradiotherapy.[41,42] Performing surgical resection after chemoradiotherapy to further improve outcomes is controversial. In the INT0139 trial, patients with N2 disease were randomized to receive concurrent chemotherapy (cisplatin and etoposide) with radiotherapy (45 Gy), and, if there was no progression, to either undergo surgical resection or continue on radiation to a total of 61 Gy. There was no difference in OS between the 2 groups; however, in an exploratory analysis, OS was improved for patients who underwent lobectomy but not pneumonectomy.[43] Therefore, chemoradiotherapy for locally advanced NSCLC remains standard of care, but lobectomy following chemoradiotherapy may be an option for selected patients.

In locally advanced NSCLC, the use of targeted agents in combined modality treatment has recently been pursued, with disappointing results. Cetuximab was given with chemoradiation in the RTOG 0617 trial with no difference in survival.[33] In the SWOG S0023 trial, an unselected patient population with inoperable stage III disease received concurrent chemoradiotherapy with cisplatin and etoposide followed by consolidation docetaxel. Patients were then randomized to receive either maintenance gefitinib or placebo. The trial was closed prematurely because OS in the gefitinib group was significantly worse (23 months vs 35 months for placebo).[44]

ADVANCED NSCLC

Palliative chemotherapy – first line

In the 1980s, a multicentre Canadian trial indicated that palliative platinum-based chemotherapy improved survival over best supportive care, prolonging OS from 4 to 8 months.[45] Practice only really started to change after 1995, however, with the publication of the Non-Small Cell Lung Cancer Collaborative Group meta-analysis[22] showing a 27% reduction in the risk of death with palliative platinum-based chemotherapy, although the improvement in median survival was only 6 weeks. The incorporation of newer chemotherapeutic agents as part of the platinum doublet further improved response rates and survival,[46] and there is now a range of acceptable options.[47-49]

Recent chemotherapeutic trials have resulted in only modest improvements in OS, however systemic therapy is constantly evolving and personalized cancer treatment holds out new hope for improved outcomes (see **Table 1**). Management will be influenced by the presence or absence of EGFR and ALK mutations, making it essential to determine the specific histologic subtype at the time of diagnosis.

For patients without an identifiable actionable mutation, standard first-line therapy consists of 4 to 6 cycles of a platinum-based doublet with one of the new agents.[46] While strong recommendations cannot be made for any one specific regimen,[49,50] some agents appear to perform better for particular histologies. In a group of patients with NSCLC treated with first-line cisplatin and either pemetrexed or gemcitabine, those with squamous cell carcinoma had inferior survival with pemetrexed (9.4 vs 10.8 months) while those with adenocarcinoma had improved survival with pemetrexed (12.6 vs 10.9 months).[48] As such, many clinicians favour using pemetrexed in the first line for patients with adenocarcinoma-subtype NSCLC. Meta-analysis data indicate that cisplatin may have superior response rates compared to carboplatin, though results are mixed, survival appears to be similar, and better response may come at the expense of increased toxicity.[51-53]

Two monoclonal antibody-based therapies have been shown to modestly improve survival when added to chemotherapy in the first line, though they are not routinely used in Canada. Bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), has been assessed in 2 phase III trials in advanced non-squamous NSCLC. ECOG 4599 randomized patients to carboplatin plus paclitaxel with or without bevacizumab,[54] finding that bevacizumab was associated with significantly improved OS and PFS, but also more treatment-related deaths (15 vs 2) and

TABLE 1: Clinical trials of agents showing survival benefit in NSCLC

	Year	Trial	Author	Intervention	N	OS (months)
First-line chemotherapy	1988	NCIC CTG trial	Rapp	VP vs CAP vs BSC	251	32.6 weeks vs 24.7 weeks vs 17 weeks
	1995	NSCLC Collaborative Group metaanalysis	NSCLC Collaborative Group	cisplatin-based chemo vs BSC	778	improvement by 1.5 months approx 4.5 months vs 6 months
	2001	SWOG	Kelly	VC vs PC	202	8 vs 8
	2002	ECOG	Schiller	cis/pacl cis/gem cis/doc carbo/pac	1155	7.8 vs. 8.1 vs. 7.4 vs. 8.1
	2008		Scagliotti	cis/pem vs cis/gem	1725	10.3 vs 10.3
First-line targeted therapy with chemotherapy	2006	ECOG 4599	Sandler	carbo/pacl +/– bevacizumab	878	12.3 vs 10.3
	2009	FLEX	Pirker	cis/vino +/– cetuximab	1125	11.3 vs 10.1
	2014 (abstract)	SQUIRE	Thatcher	cis/Gem +/– necitumumab	1093	11.5 vs 9.9
Maintenance therapy	2009	H3E-MC-JMEN	Ciuleanu	pemetrexed (switch)	663	13.4 vs 10.6
	2009		Fidias	docetaxel (switch)	566	12.3 vs 9.7 (p=0.0853)
	2010	SATURN	Cappuzzo Coudert	erlotinib (switch)	889	11.9 vs 9.6 in SD group
	2012	PARAMOUNT	Paz-Ares	pem (continuation)	1022	13.9 vs 11.0
	2013	AVAPERL	Barlesi	bevacizumab +/– pem (continuation)	376	15.7 vs NR (p=0.23)
Second- and third-line therapy	2000	TAX 317	Shepherd	doc vs BSC	103	7.0 vs 4.6
	2004	JMEI	Hanna	pem vs doc	571	8.3 vs 7.9
	2005	BR.21	Shepherd	erlotinib vs BSC	731	6.7 vs 4.7
	2014	REVEL	Garon	doc +/– ramucirumab	1253	10.5 vs 9.1
	2014	LUME-Lung 1	Reck	doc +/– nintedanib	1314	12.6 vs 10.3 (adenocarcinoma)
EGFR mutation	2009	IPASS	Mok	gefitinib vs car/pacl	1217	18.6 vs 17.3 PFS: 5.7 vs 5.8
	2010	WJTOG3405	Mitsudomi	gefitinib vs cis/doc	177	PFS: 9.2 vs 6.3
	2010		Maemondo	gefitinib vs car/pacl	230	30.5 vs 23.6 PFS: 10.8 vs 5.4
	2011	OPTIMAL, CTONG-0802	Zhou	erlotinib vs car/gem	165	PFS: 13.1 vs 4.6
	2012	EURTAC	Rosell	erlotinib vs chemo	174	19.3 vs. 19.5 PFS: 9.7 vs 5.2
	2013	LUX-Lung 3	Sequist	afatinib vs cis/pem	345	16.6 vs. 14.8 PFS: 11.1 vs 6.9
	2014	LUX-Lung 6	Wu	afatinib vs cis/gem	364	22.1 vs. 22.2 PFS: 11.0 vs 5.6
	2015	LUX-Lung 3 and 6 combined analysis	Yang and Wu	afatinib vs cis/pem afatinib vs cis/gem	709	25.8 vs 24.5 (all patients) 31.7 vs 20.7 (del19 mutation)
ALK rearrangement	2013	PROFILE 1007	Shaw	crizotinib vs pem or doc (second line)	347	20.3 vs. 22.8 PFS: 7.7 vs 3.0
	2014	PROFILE 1014	Solomon	crizotinib vs [cis/car]/pem (first line)	343	NR vs. NR PFS: 10.9 vs 7.0
	2014	ASCEND-1 (phase 1)	Shaw	ceritinib (68% post-crizotinib)	130	PFS: 7.0 ORR: 58%

ALK: anaplastic lymphoma kinase; BSC: best supportive care; CAP: cyclophosphamide/doxorubicin/cisplatin; car: carboplatin; cis: cisplatin; doc: docetaxel; EGFR: epidermal growth factor receptor; gem: gemcitabine; NSCLC: non-small cell lung cancer; NR: not reached; ORR: overall response rate; pac: paclitaxel; pem: pemetrexed; PC: paclitaxel/carboplatin; SD: stable disease; VC: vinorelbine/cisplatin; VP: vindesine/cisplatin.

toxicity. In the AVAiL trial, patients were randomized to treatment with cisplatin plus gemcitabine with either low-dose or high-dose bevacizumab or placebo.[55] Improved PFS was seen with both dosages, however there was no improvement in OS. Cetuximab, a monoclonal antibody targeting EGFR, was studied in the phase III FLEX trial, which demonstrated an improvement in OS (11.3 vs 10.1 months) when cetuximab was added to cisplatin and vinorelbine in patients with advanced NSCLC.[56]

Improvements in outcomes for squamous cell carcinoma of the lung have been difficult to achieve. Recently, however, the SQUIRE trial involving patients with advanced squamous cell NSCLC demonstrated that adding necitumumab, an anti-EGFR monoclonal antibody, to cisplatin plus gemcitabine in first-line treatment improved OS from 9.9 to 11.5 months.[57] The number of thromboembolic events was greater in the necitumumab group. A companion trial of necitumumab in nonsquamous NSCLC was negative,[58] and it remains uncertain whether this agent will be incorporated into standard therapy.

MAINTENANCE THERAPY

In an effort to improve outcomes and maximize treatment without the cumulative adverse effects of platinum chemotherapy, a strategy of maintenance therapy has emerged over the last decade. Several trials have shown that in appropriately selected patients with at least stable disease, treatment with a nonplatinum therapy upon completion of first-line therapy can improve PFS and OS. The switch maintenance strategy entails switching from a platinum doublet to a different non-cross-resistant chemotherapeutic or targeted agent. In this setting, pemetrexed (JMEN)[59] and erlotinib (SATURN)[60,61] maintenance therapy demonstrated significantly superior OS and PFS compared to placebo, while docetaxel[62] was associated with a significantly improved PFS and a trend toward superior OS when given immediately after first-line therapy rather than on progression. The continuation maintenance strategy is used when a patient continues one of the agents used in induction therapy. In the PARAMOUNT trial, continuation of pemetrexed after 4 cycles of induction with cisplatin and pemetrexed led to significantly improved PFS (4.1 vs 2.8 months) and OS (16.9 vs 14 months).[63,64] Similarly, in AVAPERL, continuation of bevacizumab and pemetrexed after initial treatment with cisplatin, pemetrexed and bevacizumab demonstrated significantly improved PFS and a trend toward improved OS compared to continuation of bevacizumab alone.[65] While maintenance therapy has been incorporated into current standard of care options, debate continues as to its value. Decisions should be made on an individual basis, with consideration of the potential toxicity and impact on quality of life in this generally poor-prognosis population.

Second-line systemic therapy

Beyond first-line therapy, only a few available treatments have been shown to improve survival. The TAX 317 trial demonstrated that patients who had previously been treated with 1 or more lines of chemotherapy had improved OS with the use of docetaxel as compared to best supportive care (7.0 vs 4.6 months).[66] In NCIC CTG BR.21, erlotinib as a single agent was shown to improve survival (6.7 vs 4.7 months)[67] when compared to best supportive care in patients who were not considered candidates for further cytotoxic chemotherapy but had already received at least 1 line of chemotherapy. Pemetrexed could be used in this setting, as its clinical efficacy is equal to docetaxel with less toxicity.[68]

Recently, 2 phase III trials have demonstrated modestly improved survival with antiangiogenic agents added to docetaxel. Ramucirumab, in the REVEL trial,[69] and nintedanib, in the LUME-Lung-1 trial[70] improved survival when added to docetaxel in the second line. Neither of these drugs has yet been approved for use in Canada, but may become therapeutic options in the coming year or two.

Immune checkpoint inhibitors, including programmed death 1 (PD1) and programmed death ligand 1 (PDL1) inhibitors, are actively being studied and are likely to be considered for use in advanced NSCLC following first line therapy.

TARGETED THERAPY

Arguably the most significant recent development in the treatment of NSCLC has been the institution of targeted therapy for patients with identifiable and actionable driver mutations. Therapies targeting EGFR and ALK rearrangement mutations are now approved and readily available, and intensive efforts are underway to identify and target new oncogenic drivers.

Companion diagnostic testing is important to identify those patients who will benefit from treatment with a targeted agent. Genetic mutations, rearrangements, fusions and amplification can be identified via multiple validated methods. Immunohistochemistry (IHC), reverse transcriptase-polymerase chain reaction (RT-PCR), and fluorescence in situ hybridization (FISH) tests, which are commonly used in clinical practice, have been developed as single gene molecular diagnostic assays for driver mutations in NSCLC. Multiplex testing for gene mutations and next generation sequencing have the ability to test multiple genes at one time, though their regular use in the clinical setting is limited by cost, time and availability. Currently, molecular testing for EGFR and ALK mutations is routinely performed across Canada upon diagnosis of advanced NSCLC; however, these tests are only performed at select locations, and tissue often needs to be sent away for analysis.

EGFR

EGFR mutations are present in approximately 15% of Caucasians and 40% of Asians. Characteristics most commonly associated with EGFR mutations include Asian descent, never or light remote smokers, female sex and adenocarcinoma histology. The IPASS trial, published in 2009, was pivotal in demonstrating that an EGFR mutation predicted response to gefitinib.[71] This phase III study, undertaken in Asia with nonsmokers and former light smokers, randomized patients to receive gefitinib or carboplatin plus paclitaxel as first-line therapy for advanced pulmonary adenocarcinoma. Results showed significantly improved PFS in the

gefitinib arm (HR 0.74, 0.65–0.85). Importantly, in patients known to have an EGFR mutation, PFS was significantly longer with gefitinib (HR 0.48, 0.36–0.64), while the effect in patients without EGFR mutation was actually detrimental (HR 2.85, 2.05–3.98). The IPASS trial changed practice, and subsequent studies of EGFR tyrosine-kinase inhibitors (TKIs) mandated that patients have known EGFR mutation for enrollment. Multiple randomized phase III trials utilizing first-generation EGFR TKIs (gefitinib[72,73] and erlotinib[74,75]) and the second-generation TKI, afatinib,[76,77] have consistently demonstrated a significant improvement in PFS compared to chemotherapy. OS remains similar between treatment groups, most likely as a result of crossover post progression, however a pooled analysis of the 2 afatanib trials (LUX-Lung 3 and 6) demonstrated an improved OS only in patients with del19 EGFR mutations.[78] As a result of consistently improved PFS, response rates and improved tolerability, standard first-line therapy for patients with EGFR mutation is now an EGFR TKI. The optimal choice of first-line TKI may become clearer with results of the LUX-Lung 7 trial (NCT01466660) comparing afatinib to gefitinib in this setting.

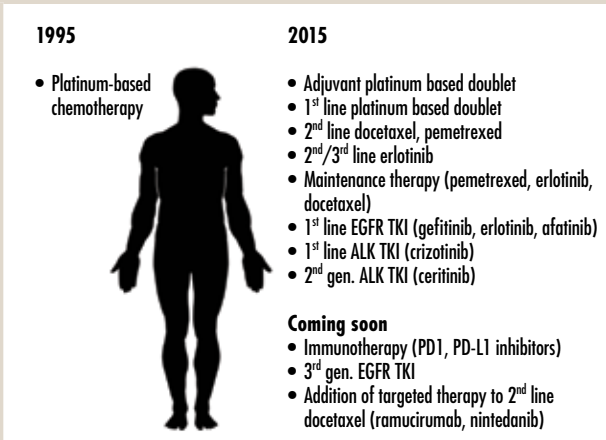
Despite overall success with first-line EGFR TKIs, patients will invariably develop resistance. EGFR T790M mutations represent the most common resistance mechanism.[79] Third-generation EGFR TKIs, which irreversibly inhibit both EGFR sensitizing mutations and T790M resistance mutations, are currently being developed and evaluated for their ability to overcome this resistance. AZD9291 has shown clinical efficacy and tolerability in a phase I trial of pretreated patients with EGFR mutation, particularly in, but not limited to, those with T790M mutation.[80] Phase II (NCT02094261) and phase III (NCT02151981) trials are now underway. Clinical trials are also in progress for 2 other third generation TKIs, CO-1686 (rociletinib) and HM61713. Another resistance mechanism is c-MET overexpression, accounting for approximately 5% to 10% of resistance to EGFR TKIs.[81] It is currently being targeted with new agents in clinical trials.

ALK

Echinoderm microtubule-associated protein like 4 (EML4)-ALK rearrangement on chromosome 2 creates a novel oncogene causing downstream signaling from ALK, which promotes tumour cell proliferation and survival.[82] ALK mutation is present in approximately 4% of patients with adenocarcinoma, and is seen more frequently in never or former light smokers as well as younger patients. Crizotinib, a small molecule TKI that was initially developed as an inhibitor of c-MET, was found to also be a potent inhibitor of ALK. It was the first drug to be approved for the treatment of patients with ALK-mutated NSCLC, after trials showed it to be superior to chemotherapy with respect to PFS and quality of life after first-line therapy.[83] More recently, in a phase III trial in the first-line setting, crizotinib was associated with improved PFS (HR 0.45, 0.35–0.60) as compared to a platinum doublet.[84] Similar to trials of EGFR TKIs, no difference in OS has been observed, likely due to crossover.

Resistance to crizotinib ultimately develops and other therapies are in development to improve subsequent treatments. Ceritinib, a novel second-generation ALK inhibitor with greater antitumour potency than crizotinib, was recently approved by Health Canada based on the ASCEND-1 phase I study. It has demonstrated a high level of activity in both pretreated and ALK inhibitor-naive patients (ORR 56% in pretreated crixotinib cohort and 62% in naive cohort).[85] Other second-generation ALK inhibitors, including alectinib and AP26113, among others, are also under investigation, with promising initial results.

FIGURE 1. Approved systemic therapies for NSCLC



ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; NSCLC non-small cell lung carcinoma; TKI: tyrosine kinase inhibitor.

ROS1

In addition to inhibiting ALK and c-MET, crizotinib also acts as a ROS1 inhibitor. ROS1 rearrangements occur in just 1% of patients with NSCLC. Similar to patients with ALK and EGFR mutated NSCLC, ROS1 rearrangements are more common in those who are never or former light smokers and in adenocarcinoma histology.[86] In a recently published expansion phase of a phase I trial, 50 patients with ROS1 mutation were treated with crizotinib, with encouraging results: the overall response rate was 72% and the median duration of response was 17.6 months.[87]

The search for actionable mutations continues. Several other genetic alterations have been identified and attempts at targeting these mutations to produce anticancer effects are ongoing. These include HER2-activating mutations, BRAF-activating mutations, MET amplification, FGFR1 amplification, RET translocations and MEK1 mutations.[88]

IMMUNOTHERAPY

Dubbed as "Breakthrough of the Year" in 2013 by *Science* magazine[89] and drug of the year by the *European Journal of Cancer*,[90] cancer immunotherapy is changing the landscape of systemic therapy. At this time, development and trials are ongoing for monoclonal antibodies, checkpoint inhibitors, therapeutic vaccines and adoptive T-cell transfer. At the forefront of immunotherapy for NSCLC are the immune checkpoint inhibitors. The programmed death pathway

mediates immunosuppression via T cells and can be overtaken by tumour cells. The PDL-1 ligand expressed on tumour cells binds to PD1 on T cells to inhibit T-cell activation and response. Both PD1 (nivolumab, pembrolizumab) and PDL1 (MPDL3280A, MEDI-4736) inhibitors have been developed and show promising outcomes when used alone or in combination with other therapies. Based on Check-Mate 017, a phase III trial comparing nivolumab to docetaxel as second-line therapy in patients with advanced squamous NSCLC, nivolumab was just approved by the FDA for this indication. The trial demonstrated a 44% reduction in the risk of death (HR 0.59, 0.44–0.79) with a median OS of 9.2 vs 6 months. Importantly, this included some patients with durable response (NCT01642004). The results of other immunotherapy trials are anxiously awaited. While these drugs are not yet available in Canada outside of clinical trials, it would seem highly likely that they will become part of the lung cancer formulary soon. However it may take some time to identify the optimal patient group or setting of therapy.

CONCLUSION

Over the past two decades, the landscape of NSCLC has been transformed. Diagnostic procedures have become more precise and less invasive. Local treatments have become increasingly effective and available to a broader range of patients. Systemic therapies have exploded in number and type and are moving toward a personalized approach (see **Figure 1**, page 17). With each of these advances, the survival of patients with NSCLC has slowly improved. Moving forward, as part of the lung cancer community, we must also advocate for our patients in order to ensure their access to the ongoing advances in the field and ultimately to better outcomes.

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