First-Line Therapy for Non-Small Cell Lung Cancer Including Targeted Therapy: A Brief Review

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Abstract

Operative removal of non-small cell lung cancer remains the mainstay of therapy. When this is not possible, cytotoxic chemotherapy and/or radiotherapy can be given but are marginally effective in prolonging overall survival. However, with a better understanding of the pathobiology of the lung cancer cells, new targeted therapies have been developed which may produce dramatic responses in selected patients. This brief review will emphasize these newer therapies in this rapidly evolving field.

Introduction

Lung cancer is extremely common and remains by far the most frequent cause of cancer-related death with approximately 154,050 deaths estimated to occur during 2018 (1). Although lung cancer deaths have declined in men, the deaths have risen in women and now account for nearly half of all women’s cancer deaths (1). Unfortunately, the vast majority are diagnosed with advanced, unresectable disease that remains incurable (1). Overall the five-year survival rate is <1% for advanced (stage IVB) disease, while the five-year survival rate for all stages is approximately 15% (1).

Data linking cigarette smoking to human lung cancer is incontrovertible (2). The risk increases with both the amount of smoking and the duration of smoking (2). Passive or second-hand smoke is also associated with an increase in the risk of lung cancer, although this increase is far lower than that observed with active smoking (2). Smoking cessation clearly decreases the risk of lung cancer (2).

Primary lung cancers can be divided into two main types based on their histology, small cell lung cancer and non-small cell lung cancer (NSCLC) (3). NSCLC constitute about 85% of lung cancers with the rest consisting of small cell and some rarer cancers (3). A basic understanding of the pathobiology of NSCLC has shown that the tumor cells depend on the formation of new blood vessels (angiogenesis), transfer of a phosphate group from ATP to tyrosine on proteins (tyrosine kinase), and regulation of programmed death ligands (checkpoint proteins) (4). Targeted therapy against these pathobiologic processes have shown dramatic effects in some NSCLC patients (4).

NSCLC is divided into 4 stages designated by roman numerals (5). The stages are based on the size of the tumor; whether it has metastasized locally or distally; and use
the TNM classification where T designates tumor size; N regional lymph node metastasis; and M distant metastasis. Stages I and II are limited to the chest but stage III has metastasized to the pleura and/or regional lung lymph nodes. Stage IIIA means the cancer has metastasized to lymph nodes that are on the same side of the chest as the cancer (ipsilateral) while stage IIIB signifies metastasis to lymph nodes on the opposite side of the chest (contralateral). Stage IV denotes there are distant metastasis outside the chest. The above is admittedly an oversimplification and there are subtle nuances that define the stages which can be found at the National Cancer Institute website (5).

An overall summary of standard preferred by the National Cancer Institute for NSCLC by stage is shown in Table 1 (6).

Table 1. Standard preferred therapy for NSCLC by stage (6).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Standard Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>II</td>
<td>Lobectomy with lymph node removal</td>
</tr>
<tr>
<td>IIIA</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Radiation therapy</td>
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<tr>
<td>IIIB</td>
<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>IV</td>
<td>Targeted therapy</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy or surgery of selected metastases</td>
</tr>
</tbody>
</table>

Surgery

Operative removal of the lung cancer is the cornerstone of management for patients with early-stage (stages I–II) NSCLC and selected patients with stage IIIA disease (7). Lobectomy is the operation of choice for localized NSCLC based on a randomized trial of lobectomy versus more limited resection (8). Operative intervention should be offered to all patients with stage I and II NSCLC who clinically are medically fit for surgical resection. However, patients may be unable to undergo a lobectomy for a variety of reasons such as: 1. severely compromised pulmonary function; 2. multisystem disease making lobectomy excessively hazardous; 3. advanced age; or 4. refusal of the operation. Some patients who cannot tolerate a full lobectomy but may be able to tolerate a more limited sublobar operation (6). For patients in whom complete tumor resection cannot be achieved with lobectomy, sleeve lobectomy is recommended over pneumonectomy because it preserves pulmonary function (6). In addition, the question of whether video-assisted thorascopic surgery (VATS) is equivalent to thoracotomy for patients with lung cancer comes up often, particularly in patients that are less than ideal surgical candidates. In a series of 741 patients with stage IA NSCLC, 5-year survival was similar but VATS was associated with fewer complications and a shorter length of
hospital stay (9). Therefore, VATS is an optional surgical approach particularly in poorer risk patients.

**Radiotherapy**

Although lobectomy is the treatment of choice for NSCLC patients with early-stage disease, some are unable to undergo an operation due to reasons listed above. For those patients, radiotherapy can be administered with curative intent, albeit with lower overall survival rates when compared to surgery (10,11).

The radiation oncology community is excited about the potential of stereotactic body radiation therapy (SBRT) (12,13). SBRT is a type of external radiation therapy that uses special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). Although there is no data yet, trials are ongoing comparing SBRT with surgery in early stage NSCLC.

**Adjuvant Therapy**

*Adjuvant chemotherapy.* Adjuvant chemotherapy is chemotherapy that is given in addition to either surgical and/or radiation therapy. Data from recent randomized adjuvant clinical trials and a meta-analysis support the use of adjuvant chemotherapy in NSCLC (14). A 5.4% five-year survival benefit was observed in a meta-analysis of five randomized trials compared to observation. Not surprisingly, the survival benefit varied according to stage but the benefit was most pronounced for patients with stage II and IIIA disease. Survival benefit in patients with stage IIB disease did not reach statistical significance. Importantly, patients with stage IA disease appeared to do worse with adjuvant chemotherapy, and therefore, is not currently recommended.

*Adjuvant radiotherapy.* The PORT meta-analysis of 2,128 patients demonstrated that the use of post-operative radiotherapy was associated with a detrimental effect on survival (15,16). The decrease in survival was more pronounced for patients with lower nodal status. The PORT meta-analysis has been criticized for its long enrolment period and use of different types of machines, techniques and radiation doses. Despite these criticisms, three randomized phase III trials support the PORT meta-analysis’ conclusion that the use of post-operative radiotherapy provides no survival benefit (17-19). For patients with N2-positive disease, however, a retrospective analysis demonstrated higher survival for those patients who had received post-operative radiotherapy (20). On the basis of the above studies, most do not recommend routine post-operative radiotherapy with the possible exception of those with N2 disease.

**Locally Advanced Disease**

About a third of patients with NSCLC present with disease that remains localized to the thorax but may be too extensive for surgical treatment (stage III) (21). Concurrent chemotherapy and radiation therapy is considered the standard therapy for this situation but results in only a modest, although statistically significant, survival benefit compared
with sequential administration (21). However, significant toxicity results from this approach and so it is usually offered only to those with good performance status.

Surgery after chemotherapy in patients with N2 disease was tested in two randomized trials. A European trial used three cycles of cisplatin-based chemotherapy, then randomized the patients to surgery or sequential thoracic radiotherapy (22). There was no significant difference in overall survival or progression-free survival. An American trial used a slightly different protocol (23). Patients with N2 disease were given two cycles with concurrent radiotherapy and then randomized to further radiation or surgery. This trial showed a better progression free survival with surgery but no difference in overall survival.

**Metastatic Disease**

About 40% of patients with NSCLC present with advanced stage IV disease. Until recently, cytotoxic chemotherapy was the cornerstone of treatment for stage IV disease but is now recommended as first line therapy alone only for patients with low or no expression of markers for targeted therapy (24). Unfortunately, in stage IV NSCLC standard cytotoxic chemotherapy alone is minimally effective. A meta-analysis that included 16 randomized trials with 2,714 patients demonstrated that cytotoxic chemotherapy offers an overall survival advantage of only 9% at 12 months compared with supportive care (25). Two-drug chemotherapy (doublets) appears to be superior to either a single agent or three-drug combinations (26). Cisplatin-based doublets are associated with a marginal one-year survival benefit compared with platinum-free regimens (27). Platinum-free regimens can be given as an alternative especially in patients who cannot tolerate platinum-based treatment (24). Although gemcitabine, vinorelbine, paclitaxel or pemetrexed are often added to either cisplatin or carboplatin, the choice of the second drug does not appear to matter in increasing survival (28).

**Targeted Therapies**

Starting in the early 2000s, NSCLC subtypes have evolved from being histologically described to molecularly defined. The use of targeted therapies in lung cancer based on molecular markers is a very rapidly changing field. At the time this article was being written (February 2018) the information was current but recommended therapies are likely to change with development of new therapies and research. It is important to point out that despite these advances, there remains no cure for stable IV NSCLC. Table 2 represents a summary of targets and targeted therapy along with the American Society of Clinical Oncology (ASCO) recommendations for stage IV NSCLC as of February 2018 (24).

Table 2. Targets and targeted therapies for NSCLC (24).

<table>
<thead>
<tr>
<th>Target</th>
<th>Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal growth factor receptor (EGFR) tyrosine kinase</td>
<td>Gefitinib, Erlotinib, Afatinib</td>
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</table>
Epidermal growth factor receptor (EGFR) | Cetuximab*  
---|---  
EGFR Thr790Met point mutation (T790M) | Osimertinib  
Vascular endothelial growth factor (VEGF) | Bevacizumab*  
Receptor tyrosine kinase 1 (ROS1) | Cizotinib, Ceritinib*  
Anaplastic lymphoma kinase (ALK) | Cizotinib  
Programmed cell death protein 1 (PD-1) | Pembrolizumab, Nibolumab*  
Programmed death-ligand 1 (PD-L1) | Atezolizumab*, Avelumab*, Durvalumab*  
*Currently not recommended for clinical use by ASCO.

The need for adequate tissue to perform molecular studies creates challenges for pulmonologists doing bronchoscopic procedures. Whereas it was previously adequate to obtain diagnostic material. However, it is now important to obtain adequate tissue to perform additional molecular testing to allow determination of whether targeted therapies are appropriate. Sometimes tissue is inadequate which might necessitate a second procedure if clinically warranted.

**Vascular Growth Factors**

*Epidermal Growth Factor Receptor (EGFR).* The EGFR pathway represents the pioneer of personalized medicine in lung cancer. EGFR is a transmembrane receptor that is highly expressed by some NSCLCs. Binding of ligands (epidermal growth factor, tumor growth factor-alpha, betacellulin, epiregulin or amphiregulin) to the extracellular EGFR domain results in autophosphorylation through tyrosine kinase activity (29). This initiates an intracellular signal transduction cascade that affects cell proliferation, motility and survival (29). Inhibition of ligand and EGFR binding or the activation of tyrosine kinases inhibit the downstream pathways resulting in inhibition of cancer cell growth (29).

Initial studies showed that most patients with NSCLC had no response to the tyrosine kinase inhibitor (TKI), gefitinib, which targets phosphorylation of EGFR (30). However, about 10 percent of patients had a rapid and often dramatic clinical response (30). An explanation for these results occurred with the identification of mutations of the tyrosine kinase coding domain (exons 18–21) of the EGFR gene. Subsequent research linked these mutations to the clinical response to gefitinib (31,32). Although about 10% of Caucasian NSCLC have these mutations, the mutations were observed more commonly in Asian patients, particularly non-smoking women (33). There is now overwhelming and consistent evidence from multiple trials that all the approved EGFR-TKIs (gefitinib, erlotinib, or afatinib) have greater activity than platinum-based chemotherapy as the first-line treatment of patients with advanced NSCLC with activating EGFR mutations (24). These agents have more favorable toxicity profiles than platinum-based chemotherapy and have demonstrated improvements in quality of life. The choice of which EGFR-TKI to recommend to patients should be based on the availability and
toxicity of the individual therapy. Randomized clinical trials are ongoing comparing EGFR-TKIs. The results of these trials may help refine this in the future.

Despite high tumor response rates with first-line EGFR-TKIs, NSCLC progresses in a majority of patients after 9 to 13 months of treatment. At the time of progression, approximately 60% of patients (regardless of race or ethnic background) are found to have a Thr790Met point mutation (T790M) in the gene encoding EGFR (34). The presence of the T790M variant reduces binding of first-generation EGFR-TKIs to the leading to disease progression (34). Osimertinib is an irreversible EGFR-TKI that can bind to EGFR despite the T790M resistance mutations and has recently become clinically available (35). Currently it is recommended for T790M mutations that occur after the first-line EGFR-TKIs have failed (24).

Cetuximab is a monoclonal antibody directed against EGFR itself. In the past, addition of cetuximab to cisplatin doublet chemotherapy in EGFR positive tumors was usual. However, cetuximab has recently been shown to shorten progression free survival with some adverse effects and is no longer recommended (24).

*Vascular endothelial growth factor (VEGF).* Angiogenesis, the formation of new blood vessels, is a fundamental process for the development of solid tumors and the growth of secondary metastatic lesions. Vascular endothelial growth factor (VEGF) acts to promote normal and tumor angiogenesis. Bevacizumab, a recombinant, humanized, monoclonal antibody against VEGF, was previously recommended as first-line therapy in stage IV NSCLC patients without a contraindication. However, the most recent ASCO guidelines finds insufficient evidence to recommend bevacizumab in combination with chemotherapy as first-line treatment (24).

*Other Kinase Inhibitors.* Receptor tyrosine kinase 1 (ROS1) and the structurally similar anaplastic lymphoma kinase (ALK) are enzymes that are critical regulators of normal cellular activity. In NSCLC rearrangements of these genes can cause them to act as oncogenes, or genes that transform normal cells into cancer cells. Rearrangements in the ROS1 or ALK genes are found in a small percentage of patients with NSCLC. Crizotinib is a molecule that blocks both the ROS1 and ALK proteins. Crizotinib reduced tumor size in ALK+ or ROS1+ positive patients although the most recent ASCO guidelines consider the evidence only moderate with ALK+ and weak with ROS1+ patients (24,36-8).

*Checkpoint Inhibitors.* An important part of the immune system is its ability to tell the difference between normal cells and those that are “foreign”. To do this, it uses “checkpoints”, molecules on certain immune cells that need to be activated (or inactivated) to start an immune response (39). NSCLC can use these checkpoints to avoid being attacked by the immune system. Programmed cell death protein 1 (PD-1) is a checkpoint protein on T cells. It normally acts as an “off switch” when it attaches to programmed death-ligand 1 (PD-L1), a protein on some normal (and cancer) cells. Some NSCLCs have large amounts of PD-L1, which helps them evade immune attack. Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost
the immune response against NSCLC cells. In patients with NSCLC with >50% of their tumor cells PD-1+ (tumor proportion score >50%), pembrolizumab, a monoclonal antibody against PD-1, significantly prolonged progression-free and overall survival compared to platinum-based chemotherapy (40). Based on this trial, pembrolizumab is now recommended by ASCO for patients with a tumor proportion score >50% for PD-1 (23). A number of other PD-1 (e.g., nivolumab) and PD-L1 inhibitors (e.g., atezolizumab, avelumab, durvalumab) exist but ASCO recommends only pembrolizumab at this time (39,40). As more of these checkpoint inhibitors are developed and tested this will likely change.

Second and Third-Line NSCLC Therapy

Second and third-line therapy for NSCLC is beyond the scope of this brief review. It is a rapidly evolving field which should include close collaboration between the pulmonologist, oncologist and other members of the patient’s NSCLC treatment team.

After an initial response, lung cancers can become resistant to therapy. One example mentioned above is the development of the T790M mutation in EGFR+ NSCLC. In selected instances rebiopsy of the primary tumor or metastases can direct a new, effective therapy. Obviously, it is not possible to rebiopsy every NSCLC patient after failure of the initial therapy. However, other techniques are being investigated. One is liquid biopsy where blood is drawn and subjected to molecular techniques to determine a possible cause for tumor resistance. Multiple liquid biopsy molecular methods are presently being examined to determine their efficacy as surrogates to the tumor tissue biopsy (41).

Future Directions

The combination of a variety of existing therapies for NSCLC is being evaluated. These will likely yield revised recommendations for therapy. In addition, a variety of therapies, both existing for other cancers, or newer therapies in development are being tested. These include both monoclonal antibodies and biologic inhibitors (Table 3).

Table 3. Potential new targeted therapies for NSCLC (42,43).

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Target</th>
<th>Antibody</th>
</tr>
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<tbody>
<tr>
<td>Anti-IGF 1 receptor (IGF-1R)</td>
<td></td>
<td>Figitumumab</td>
</tr>
<tr>
<td>Anti-NR-LU-10</td>
<td></td>
<td>Nofetumomab</td>
</tr>
<tr>
<td>Anti-epidermal growth factor receptor (EGFR)</td>
<td></td>
<td>Nimotuzumab, Ficlatuzumab</td>
</tr>
<tr>
<td>Anti- receptor activator of nuclear factor-kappa B ligand (RANKL)</td>
<td></td>
<td>Denosumab</td>
</tr>
<tr>
<td>Anti-Cytotoxic T-Lymphocyte-Associated Antigen 4</td>
<td></td>
<td>Ipilimumab, Tremelimumab</td>
</tr>
<tr>
<td>Tyrosine-protein kinase Met (C-MET) receptor</td>
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<td>Onartuzumab</td>
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### Biologic Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Inhibitor</th>
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<tbody>
<tr>
<td>Poly ADP ribose polymerase (PARP)</td>
<td>Veliparib, Olaparib</td>
</tr>
<tr>
<td>Phosphatidylinositol 3-kinase (PI3K)</td>
<td>Veliparib, Olaparib</td>
</tr>
<tr>
<td>Phosphatidylinositol 3-kinase (PI3K)</td>
<td>Buparlisib, Alpelisib</td>
</tr>
<tr>
<td>BRAF</td>
<td>Dabrafenib</td>
</tr>
<tr>
<td>MEK1/MEK2</td>
<td>Trametinib</td>
</tr>
<tr>
<td>Receptor tyrosine-protein kinase erbB-2 (HER-2)</td>
<td>Dacomitinib, Afaninib</td>
</tr>
<tr>
<td>Signal transducer and activator of transcription 3 (STAT3)</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td>Kirsten rat sarcoma viral oncogene homolog (KRAS)</td>
<td>Selumetinib</td>
</tr>
<tr>
<td>Tyrosine-protein kinase Met (C-MET) receptor</td>
<td>Tivantinib (ARQ197), Cabozantinib</td>
</tr>
<tr>
<td>Fibroblast Growth Factor Receptor (FGFR)</td>
<td>Pazopanib, Ponatinib</td>
</tr>
<tr>
<td>Phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene homolog 1/mechanistic target of rapamycin (PI3K /AKT/mTOR)</td>
<td>GDC-0941, BKM120, XL147</td>
</tr>
<tr>
<td>Proto-oncogene tyrosine-protein kinase receptor (Ret)</td>
<td>Cabozantinib, Vandetanib, Sunitinib, Sorafenib, Alectinib</td>
</tr>
</tbody>
</table>

The numbers of pathways and drugs being tested is very impressive and the clinical responses can be dramatic in some patients. One might be tempted to conclude that these therapies might result in a “cure” for NSCLC. However, most of these mutations occur in a small minority of NSCLCs. Furthermore, even if initially successful, resistance to targeted therapies may quickly develop limiting their clinical usefulness in NSCLC.

Targeted therapies may also have potential as adjuvant therapies. In support of this concept, a recent phase 3 study compared durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy (44). The progression-free survival was 16.8 months with durvalumab versus 5.6 months with placebo (p<0.001). It seems likely that more trials using targeted therapy earlier in cancer therapy will be done.

### References


