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Lung Cancer

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One third of all cancer-related deaths worldwide are caused by lung cancer, which accounts for more fatalities each year than breast, prostate, and colon cancers combined.[1]

The greatest risk of developing lung cancer is associated with tobacco use,[2] and the World Health Organization (WHO) estimates that the number of tobacco-related deaths will have exceeded 2 million per year by 2010.[3] Non-small cell lung cancer (NSCLC) is responsible for 80% of all lung cancer cases, and most patients present with inoperable locally advanced (stage III B) or metastatic (stage IV) disease. Unfortunately, the long-term prognosis for these patients remains poor because of the inability of systemic therapy to cure advanced disease. Chemotherapy has only a palliative role and a 5-year survival rate ranging from 8% to 15%.[4]Therefore, active treatment in conjunction with the minimization of side effects is a key goal.

CHEMOTHERAPY IN ADVANCED DISEASE

In the past few years, several studies have investigated the use of systemic therapy in this setting. In 1995, the NSCLC Collaborative Group's meta-analysis confirmed the palliative role of chemotherapy.[5] The results of 11 randomized trials showed that cisplatin-based chemotherapy produces 10% improvement in 1-year survival compared with best supportive care alone and determines benefits in terms of symptom control, quality of life,[6] and cost-effectiveness in advanced NSCLC.[7]

During the last 10 years, several new cytotoxic agents have become available; these include taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and topoisomerase 1 inhibitor irinotecan. Three of these new chemotherapy regimens (gemcitabine plus cisplatin, docetaxel plus cisplatin, and paclitaxel plus carboplatin) were compared with a reference doublet (paclitaxel plus cisplatin) in a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG). The conclusion was that third-generation agents can moderately improve 1- and 2-year survival rates in patients with good performance status (PS) with NSCLC. No survival differences were observed in the four treatment arms, although the carboplatin-containing doublet was associated with lower toxicity.[8]

FURTHER AREAS OF INVESTIGATION FOR CYTOTOXIC AGENTS

The major challenge of future chemotherapy in NSCLC is the increased efficacy of cytotoxic agents minimizing side effects. Pemetrexed, a multi-target anti-folate, is a novel drug recently introduced into clinical practice for the treatment of malignant pleural mesothelioma[9,10] and NSCLC, and it could play an important role in this setting. The single-agent response rates in previously untreated NSCLC are 16% to 23%,[11,12] whereas it is 39% to 45% in combination trials.[13,14]

Trials comparing doublet-containing pemetrexed with cisplatin plus gemcitabine or with placebo plus best supportive care, after prior platinum treatment, are underway. A comparison between pemetrexed plus cisplatin and a non-cisplatin–containing arm could also be interesting.[15]

PHARMACOGENOMICS

Pharmacogenomics makes it possible to select specific patients on a genetic basis. Early results indicate that the applications of genomics in NSCLC could have a significant impact on therapeutic strategies and improve the survival of particular subpopulations of patients.[16]

Several studies of pharmacogenomics concern two genes: RRM1 and ERCC1. RRM1 (ribonucleotide reductase M1 gene) has an impact on DNA damage and repair. When this gene is highly expressed, the resistance to gemcitabine is increased; when the level of RRM1 is low, cell lines become more sensitive to gemcitabine.[17] RRM1 mRNA expression could be a predictive marker of survival in patients treated with cisplatin plus gemcitabine, and genetic testing of RRM1 expression could be used to personalize chemotherapy.

Another pharmacogenomic study showed that the excision repair cross-complementing group (ERCC1) gene is related to cisplatin activity. A recent phase III trial[18] compared docetaxel plus cisplatin versus docetaxel plus gemcitabine in stage IV NSCLC and showed that increased ERCC1 mRNA levels are linked with resistance to platinum-based chemotherapy. Based on the evidence that RRM1 and ERCC1 expression may result in chemoresistence, other trials, like MADeIT, were initiated. This trial was designed to tailor chemotherapy based on the expression of these genes. Patients with high levels of RRM1 expression received a chemotherapy doublet that did not contain gemcitabine, whereas those with low levels of RRM1 were treated with gemcitab-

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ine. The goal was to demonstrate that up-front patient selection can lead to the choice of the appropriate treatment and, potentially, improve outcome.

BIOLOGICAL AGENTS

Platinum-based combination therapy is the established standard of care in the treatment of NSCLC; therefore, all approaches to first-line chemotherapy seem to have reached a therapeutic plateau. An interesting new field of cancer research is the investigation of novel biological agents able to target different cell signaling receptors. Because of its central role in tumor angiogenesis, the vascular endothelial growth factor (VEGF) and its receptor are very important targets of biological agents.

Bevacizumab is an anti-VEGF recombinant humanized monoclonal antibody that can bind and clear VEGF from the tumor microenvironment.[19] It obtains additional antitumor activity because of its effects on tumor vasculature, interstitial pressure, and blood vessel permeability.[20] In NSCLC, the high expression of VEGF is common and is associated with poor outcome.[21,22] Recent trials[23] demonstrated a statistically significant advantage in median survival favoring the combination of bevacizumab plus paclitaxel plus carboplatin versus paclitaxel plus carboplatin in the treatment of advanced chemotherapy-naïve NSCLC that presented neither hemoptysis nor central nervous system metastases. This is the first trial showing that the addition of a targeted agent to a standard cytotoxic doublet can prolong survival[24] and, in the United States, this result has led to the use of bevacizumab in first-line treatment of advanced non-squamous NSCLC. A study testing two different doses of bevacizumab (7 vs 15 mg/m^2) associated with chemotherapy has been completed recently.

MOLECULAR TARGET THERAPIES

Several targeted agents are being investigated for the treatment of patients with thoracic malignancies.

ZD6474 is an inhibitor of tyrosin kinase activity of the VEGF-2 and EGF receptors (EGFR).[25]

A randomized phase II trial has shown that the addiction of ZD6474 to docetaxel prolongs median time to disease progression when compared with docetaxel alone.[25] This encouraging result justifies further study in a phase III setting.

Sorafenib is an oral multi-kinase inhibitor that targets several serine/threonine and receptor tyrosine kinases via its effects on the RAF/MEK/ERK pathway at the level of Raf kinase, VEGFR-2 and PDGFR-ß. Several ongoing studies are evaluating the efficacy of combination chemotherapy with sorafenib. The clinical benefit of this agent has been demonstrated in a randomized, double blind, placebo-controlled phase III study among patients with renal carcinoma (RCC). Preliminary analyses of the sorafenib monotherapy data in NSCLC reveal disease-stabilizing effects similar to those observed in RCC.

However, no benefit was demonstrated in NSCLC with other biological agents such as bexarotene,[26,27] ionafarnib,[28] and aprinocarsen,[29,30] but negative results could be the result of lack of selection of patients.

Recent data have suggested that immunotherapy could have clinical utility in NSCLC. PF-3512676 is a synthetic, single-stranded oligodeoxynucleotide (ODN) molecule and is a toll-like receptor 9 (TLR-9) agonist that provides a targeted and specific modality of immunotherapy by activating plasmacytoid dendritic cells and B-lymphocytes. Data from a randomized phase II trial suggest that the addition of PF-3512676 to standard taxane/platinum chemotherapy for first-line treatment of patients with advanced NSCLC can increase objective response rate and prolong overall survival. These preliminary results indicate that PF-3512676 is able to provide a novel, safe, and effective treatment modality when combined with a platinum-based doublet, but confirmatory phase III trials are necessary.

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