Overall there is a potential for better results even due to conventional chemotherapy giving new cytotoxics or selecting patients and treatment by pharmacogenomic data.

E03-02 What's new in Systemic Therapy? Mon, Sept 3, 16:00 – 17:30

Targeted therapy for non-small cell lung cancer: beyond EGFR and VEGF

Ramalingam, Suresh S.

University of Pittsburgh, Pittsburgh, PA, USA

Lung cancer results in more than a million deaths annually worldwide (1). Non-small cell lung cancer, which comprises of adenocarcinoma, squamous cell carcinoma, bronchioloalveolar carcinoma (BAC) and large cell carcinoma, accounts for more than 80% of all cases of lung cancer. NSCLC is diagnosed at an advanced stage in a majority of the patients, for whom systemic therapy remains the mainstay of treatment. Systemic therapy also benefits patients with earlier stages of NSCLC, since micrometastasis is an early event (2, 3). The availability of newer and novel chemotherapeutic agents has contributed to both the survival and quality of life benefits for patients with advanced stage NSCLC (4-6). However, it appears that an efficacy plateau has been reached with currently available agents in both the first-line and second-line therapy of advanced NSCLC (4, 7).

Molecularly targeted agents provide the ability to modulate events that are unique to the cancer cell. Since NSCLC has wide molecular heterogeneity, a number of cell signaling pathways are potential targets for treatment (8). The targeted agents that have been actively investigated for the treatment of NSCLC include EGFR inhibitors, anti-angiogenic agents, proteosomal inhibition, inhibitors of the mammalian target of rapamycin (mTOR) pathway, matrix metalloproteinase inhibitors and protein kinase C inhibitors. Inhibitors of the EGFR and the anti-angiogenic pathway are already used for routine care of patients with advanced NSCLC and will be discussed elsewhere.

Proteosome inhibition

The 26 S proteosome is a multi-subunit protein complex that is involved in the degradation of a variety of proteins with critical functions such as regulation of the cell cycle, transcription and apoptosis (9). Bortezomib is a specific inhibitor of the 26 S proteosome that has been shown in preclinical models to induce apoptosis and enhance the efficacy of chemotherapy against a variety of cancer cell lines. It is approved for the treatment of multiple myeloma in the US. Based on promising preclinical activity, bortezomib has been evaluated for the treatment of advanced NSCLC by multiple clinical trials. In a phase II study, advanced NSCLC patients (N=155) who progressed following one prior chemotherapy regimen were randomized to treatment with bortezomib alone or in combination with docetaxel (10). The response rate was 8% with bortezomib monotherapy compared to 9% with the combination. However the median time to progression favored the combination (4 months vs. 1.5 months). In another phase II study by the SWOG, bortezomib was combined with the regimen of carboplatin and gemcitabine for first line therapy of advanced NSCLC patients (N=121) (11). The combination was tolerated well and was associated with a median survival of 11 months. The median time to progression was 5 months. Main toxicities associated with the combination included thrombocytopenia, neutropenia and neuropathy. Bortezomib has also been evaluated in combination with other targeted agents such as EGFR inhibitors by preclinical studies. Favorable results have led to early phase clinical trials with novel bortezomib-based combinations. Based on these results, bortezomib appears to be an active agent for the treatment of advanced NSCLC. Large randomized clinical trials are necessary to determine whether the addition of bortezomib to chemotherapy would result in improvements in survival for patients with advanced NSCLC.

Histone deacetylase (HDAC) inhibitors

HDAC mediates the transcription of a number of genes relevant for cell cycle regulation and apoptosis. By altering the dynamic equilibrium between histone acetylation and deacetylation, HDAC inhibitors have been noted to exert anti-cancer effects against a variety of cancer cell lines (12). The anti-cancer activity of HDAC inhibitors has also been attributed to the effects on non-histone targets such as p53, heat shock protein 90, alpha tubulin, etc. A number of novel agents that inhibit HDAC are currently under development.

Vorinostat (SAHA) is an orally administered inhibitor of HDAC that has recently been approved for the treatment of refractory cutaneous T-cell lymphoma. Early phase clinical trials with vorinostat have demonstrated activity against mesothelioma and non-small cell lung cancer (13). Vorinostat also enhances the activity of other commonly used anti-cancer agents such as the platinum compounds and the taxanes (14, 15). Therefore, we conducted a phase I study to evaluate the combination of vorinostat with carboplatin and paclitaxel (16). The study included 19 patients with previously untreated NSCLC. Vorinostat at a dose of 400 mg/day (2 weeks on, 1 week off) was combined safely with carboplatin (AUC = 6 mg/ml X min) and paclitaxel (200 mg/m^2). There were 10 objective responses and 4 had disease stabilization out of a total of 19 patients with previously untreated NSCLC. These exciting results have led to a phase II study that randomizes patients with advanced NSCLC to treatment with carboplatin and paclitaxel in combination with either vorinostat or placebo. Vorinostat is also being evaluated in combination with a number of targeted agents such as EGFR inhibitors. In particular, vorinostat has been shown to have synergistic interactions with EGFR TKI in resistant cell lines by its effects on E-cadherin (17). Therefore, a phase I/II study is being conducted to evaluate vorinostat in combination with erlotinib for second line treatment of advanced NSCLC. Several other HDAC inhibitors such as PXD 101, MS 275 and LBH 589 are also in early phase clinical trials for advanced NSCLC.

mTOR pathway

The mammalian target of rapamycin (mTOR) is a 289 kD serine/threonine kinase, that plays a central role in regulating cell growth, proliferation and survival (18). mTOR functions downstream of the PI3K/Akt pathway which is a major cell survival pathway (19). mTOR is dysregulated in several malignancies and has therefore become a target for the treatment of cancer. Agents such as CCI-779 (temsirolimus) and RAD 001(everolimus) are in various stages of clinical evaluation for the treatment of various malignancies. A phase III study conducted for patients with advanced renal cell carcinoma demonstrated survival advantage for high-risk patients treated with CCI-779 over therapy with interferon (20). This has paved the way for extensive evaluation of mTOR inhibitors as monotherapy or in combination with established agents for the treatment of various malignancies.

In lung cancer, the mTOR inhibitors are under evaluation as monotherapy and in combination with proven agents. A phase I/II study is evaluating the combination of erlotinib and RAD 001 for patients with refractory NSCLC (21). Preliminary results indicated promising anti-cancer activity, though the optimal doses are yet to be established for the combination. Another ongoing study is evaluating the combination of gefitinib and RAD 001 for advanced NSCLC in the second

or third line therapy settings. A phase IB study is evaluating the use of RAD 001 as pre-operative therapy for a brief duration followed by surgical resection with the intent of evaluating the molecular effects of this novel agent within the tumor of early stage NSCLC patients. The results of such studies will provide insight into the role of mTOR inhibitors in lung cancer therapy.

Conclusions

In addition to the agents discussed in this review, a number of agents that modulate other pathways including MEK, aurora kinase, C-met and insulin-like growth factor, are being studied for the treatment of various solid malignancies including NSCLC (24-27). As these agents enter the clinic, proper patient selection will be critical to their success. Clinical or molecular predictive markers that will help with patient selection should be evaluated as part of early phase clinical trials. With the increasing number of available new agents, enhancing accrual to clinical trials will be critical to successfully test these agents in a timely manner.

References

1. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001;2:533-43.
2. Winton TL, Livingston R, Johnson D, et al. A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage 1B and II non small cell lung cancer (NSCLC) Intergroup JBR.10. Proc Am Soc Clin Oncol 2004;23.
3. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.
5. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-8.
6. Fossella F, Pereira JR, Von Pawel J, et al. Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group. J Clin Oncol 2003.
7. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
8. Salgia R, Skarin AT. Molecular abnormalities in lung cancer. J Clin Oncol 1998;16:1207-17.
9. Schenkein DP. Use of proteasome inhibition in the treatment of lung cancer. Clin Lung Cancer 2004;6 Suppl 2:S89-96.
10. Fanucchi MP, Fossella F, Fidias P, et al. Bortezomib + docetaxel in previously treated patients with advanced non-small cell lung cancer: A phase 2 study. J Clin Oncol 2005;23:Abs# 7034, 629.
11. Davies AM, McCoy J, Lara PN, Gumerlock PH, Crowley J, Gandara DR. Bortezomib + gemcitabine (Gem)/carboplatin (Carbo) results in encouraging survival in advanced non-small cell lung cancer (NSCLC): Results of a phase II Southwest Oncology Group (SWOG) trial (S0339). J Clin Oncol 2006;24:Abs# 7017.
12. Marks PA, Richon VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. J Natl Cancer Inst 2000;92:1210-6.
13. Kelly WK, Richon VM, O'Connor O, et al. Phase I clinical trial of histone deacetylase inhibitor: suberoylanilide hydroxamic acid administered intravenously. Clin Cancer Res 2003;9:3578-88.
14. Bali P, Pranpat M, Swaby R, et al. Activity of suberoylanilide hydroxamic Acid against human breast cancer cells with amplification of her-2. Clin Cancer Res 2005;11:6382-9.
15. Kim MS, Blake M, Baek JH, Kohlhagen G, Pommier Y, Carrier F. Inhibition of histone deacetylase increases cytotoxicity to anticancer drugs targeting DNA. Cancer Res 2003;63:7291-300.
16. Ramalingam s, Parise RA, Egorin MJ, et al. Phase I study of vorinostat, a histone deacetylase (HDAC) inhibitor, in combination with carboplatin (Cb) and paclitaxel (P) for patients with advanced solid malignancies J Clin Oncol 2006;24:98s (Abs# 2077).
17. Witta SE, Gemmill RM, Hirsch FR, et al. Restoring E-cadherin expression increases sensitivity to epidermal growth factor receptor inhibitors in lung cancer cell lines. Cancer Res 2006;66:944-50.
18. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. Nat Rev Cancer 2004;4:335-48.
19. Hay N, Sonenberg N. Upstream and downstream of mTOR. Genes Dev 2004;18:1926-45.
20. Hudes G, Carducci M, Tomczak P, et al. A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC). J Clin Oncol 2006;24:Abs # LBA4.
21. Papadimitrakopoulou V, Blumenschein G, Rollins M, et al. A phase I/II study investigating the combination of RAD001(R) (everolimus) and erlotinib (E) as 2nd /3rd line therapy in patients (pts) with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy. J Clin Oncol 2006;24:Abs # 7039.
22. Fehrenbacher L, O'Neill V, Belani CP, et al. A Phase II, Multicenter, Randomized Clinical Trial To Evaluate The Efficacy And Safety Of Bevacizumab (Avastin®) In Combination With Either Chemotherapy (Docetaxel Or Pemetrexed) Or Erlotinib Hydrochloride (Tarceva®) Compared With Chemotherapy Alone For Treatment Of Recurrent Or Refractory Non-Small Cell Lung Cancer. J Clin Oncol 2006;24:Abs # 7062, 379s.
23. Naret CL, Ramalingam S, Beattie L, et al. Total blockade of the epidermal growth factor receptor with the combination of cetuximab and gefitinib: A phase I study for patients with recurrent non-small cell lung cancer (NSCLC. J Clin Oncol 2006;24:Abs # 17045.
24. Easton JB, Houghton PJ. mTOR and cancer therapy. Oncogene 2006;25:6436-46.
25. Gollob JA, Wilhelm S, Carter C, Kelley SL. Role of Raf kinase in cancer: therapeutic potential of targeting the Raf/MEK/ERK signal transduction pathway. Semin Oncol 2006;33:392-406.
26. Girdler F, Gascoigne KE, Eyers PA, et al. Validating Aurora B as an anti-cancer drug target. J Cell Sci 2006;119:3664-75.
27. Guerreiro AS, Boller D, Doepfner KT, Arcaro A. IGF-IR: potential role in antitumor agents. Drug News Perspect 2006;19:261-72.

E03-03 **What's new in Systemic Therapy? Mon, Sept 3, 16:00 – 17:30**

How do we speed up developing new agents?

Kris, Mark G.

Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Despite incremental gains improving both the quality and length of life of persons with lung cancer, cure remains elusive for nearly all patients with metastases. The need for better treatments has never been greater. To meet this challenge, advances in biology and biotechnology have provided us with hundreds of agents appropriate for testing in patients. This opportunity has brought with it the challenge to select and quickly assess which of these potential treatments will further improve the lives of patients with lung cancer and maybe even affect a cure. Despite the importance and enormity of this task, relatively little attention has been paid to the process of developing therapies to combat lung cancer.

In 1949, Karnofsky and Burchenal observed that agents that do not objectively shrink tumors cannot be expected to prolong life. Half a century of drug development has proven this assertion correct. This is especially true with therapies that lead to cure or dramatic benefit. No randomized trials were necessary to prove that etoposide was a useful treatment in SCLC. Today, our best surrogate for survival or cure remains the objective documentation of the regression of tumors on physical exam or imaging studies. Our task is to identify how to document changes in lesion size more accurately and quickly. With rare exception, the helical CT scan is the optimal way to achieve this goal. It is likely that uni- or bi-dimensional CT measurements are reliable and reproducible within 10% or less based on a study now underway. Where this has been studied with both single agent gefitinib and bevacizumab, changes in lesion size exceeding this threshold can be documented in as little as 14 or 21 days. These facts suggest at our current technology allows us to replace current response standards of demanding 30% or 50% changes to define benefit and the necessity to

