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PLENARY SESSION "Combined treatment for lung cancer: Chemical and biological radio modulation"

Promising new molecule-targeted therapies and their integration into radiotherapy for lung cancer

Mariano Provencio[a], *Francisco Valcárcel*[b]

[a] *Department of Medical Oncology, Radiation Oncology, Hospital Universitario Clínica Puerta de Hierro-Majadahonda, Madrid, Spain*
[b] *Hospital Ramón y Cajal, Madrid, Spain*

1. Introduction

Current research focuses on the development of new agents and the assessment of combination of therapies and integration of the new agents.

In this context, it becomes critically important to identify potential biological targets, the blockade of which would affect multiple downstream signaling cascades.

2. Blocking the EGFR pathway and radiotherapy

One of the most attractive pathways is the inhibition of the epidermal growth factor receptor (EGFR) signaling pathway, either through small molecules (gefitinib or erlotinib) or monoclonal antibodies (cetuximab), combined with radiotherapy. Few data exist in direct clinical results on the association between Tyrosine Kinase Inhibitors (TKIs) and radiotherapy, but data do exist that *in vitro* TKIs reinforce chemotherapy and radiation.

Cetuximab is a chimeric human–mouse monoclonal antibody that binds to the EGFR and inhibits the growth of EGFR-expressing cancer cell lines *in vitro* and *in vivo* in athymic nude mice. Radiation activates EGFR signaling, which leads to radio-resistance by inducing cell proliferation and enhancing DNA repair and synergistic activity when cetuximab was combined with radiotherapy. NSCLC cell lines[1] treated with cetuximab alone or in combination with radiation, chemotherapy or chemoradiation to determine the cooperative effects of cetuximab both *in vitro* and *in vivo* in athymic nude mice bearing NSCLC xenografts. Cetuximab could be beneficial for some patients and detrimental to others and that cetuximab sensitivity does not correlate clearly with EGFR expression levels, though it appears to need some degree of EFGR expression. However, studies are needed to establish proper safety for this therapy approach in patients with locally advanced lung cancer. Up to now, the most impressive results have been those achieved by the Radiation Therapy Oncology Group study (RTOG 0324).[2] Two-year follow-up reported median survival of 22.7 months and overall survival of 49.3%, better than any study previously reported by the RTOG.

Gefitinib has a radiosensitizing effect that was confirmed in cell lines.[3] Stinchcombe and colleagues investigated the tolerance of Gefitinib for unresectable stage III NSCLC in combination with radiotherapy. The primary toxicities of concurrent high-dose three-dimensional conformal thoracic radiotherapy were grade 3 esophagitis (19.5%) and cardiac arrhythmia (9.5%), but survival results were disappointing, with overall survival at 9 months.[4]

Evidence of treatment with erlotinib and thoracic radiotherapy is less than with gefitinib. In short, results have not been very encouraging, though there was no excess toxicity. The phase I study[5] by Choong aimed to determine the maximum tolerated dose of erlotinib administered with two standard chemo-radiotherapy regimens for non-small-cell lung cancer, but median survival times were disappointing. Epidermal growth factor receptor IHC or FISH-positive patients showed no significant overall survival difference.

3. Antiangiogenic and radiotherapy

Tumor cells produce growth factors that stimulate proliferation and migration of endothelial cells, and finally the

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formation of new blood vessels within the tumor tissue. Radiation induces cell death as a result of damage to cell membranes, DNA and microvascular endothelial cells within the tumor stroma. In response to the endothelial damage and hypoxia, tumor cells increase their expression of proangiogenic growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor.

Therefore, it is reasonable to think that a combination of antiangiogenic therapy and radiotherapy may improve tumor control. However, one must step carefully on transferring the conclusions of treatments in tumor xenograft models to patients, as even gene expression may vary, depending on the location of the grafted tumor. *In vitro* clonogenic cell-survival studies of H441 lung adenocarcinoma cells, ZD6474 treatment impaired the efficiency of the repair of sub-lethal radiation damage, even after short-term exposure of lung cancer cells to ZD6474.

There are few studies of bevacizumab with thoracic radiotherapy. The data we have from reported studies advise caution and use always of controlled clinical trials. Selection of patients is essential to avoid potentially mortal toxicity.[6]

3.1. *m-TOR pathway*

The Ras/PI3 kinase pathway with Akt is an attractive target. We know that this pathway is frequently activated by mutation of Ras or components of the pathway, and by deregulated growth factor receptor signaling to Ras. Activation of Ras signaling increases the survival of tumor cells exposed to agents that cause DNA damage. Inhibition of oncogenic Ras expression also decreases radiation survival in both cell lines to a similar degree contribute to radiation survival when activated by oncogenic mutations.

mTOR inhibition interrupts the radiation-induced stress response of tumor cells that should protect tumor microvasculature against radiation damage. In tumor cells, mTOR inhibition prevents radiation-induced expression of proangiogenic growth factors such as VEGF, reducing the angiogenic potential of tumor cells themselves. In endothelial cells, mTOR blockade disrupts the VEGF signaling pathway, leading to inhibition of endothelial cell proliferation.

mTOR is an attractive target in cancer therapy because the PI3K/Akt/mTOR pathway is frequently activated in tumors promoting cell proliferation and radiation resistance. Genetic variations in this pathway may modulate clinical outcomes and be used to build a model of individualized therapy.

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