Editorial

Immunotherapy and lung cancer: from therapeutic cancer vaccination to novel approaches

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In the last years, knowledge about immune system and cancer rapidly increased, becoming evident that immune system, when properly stimulated, can eradicate cancer cells (1,2). Immunotherapy includes two main approaches: passive and active immunotherapy. Passive immunotherapy consists in administering monoclonal antibodies targeting specific tumor-associated antigens (i.e., rituximab in lymphoma or trastuzumab in breast cancer). In lung cancer such strategy showed modest or no benefit with no agent so far approved for treatment of advanced disease. In 2009 cetuximab was not approved for first line treatment of advanced non-small cell lung cancer (NSCLC) despite the survival benefits showed by the combination of cetuximab plus chemotherapy in patients with *EGFR* mutation (3). Trials of trastuzumab or other HER2-targeted agents failed to demonstrate clinical benefit in NSCLC as monotherapy or combined with chemotherapy (4). Active immunotherapy includes therapeutic cancer vaccination (antigen specific immunotherapy), which aims to enhance T-cells response against specifically expressed tumor antigens, and immune check point inhibitors (non-antigen specific immunotherapies) which aim to "remove the brakes" on T-cells and restore the immune response against tumor cells (1,2,5).

The MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy (MAGRIT) trial was a randomized, double-blind, placebo-controlled trial aiming at investigating the efficacy of MAGE A3 cancer immunotherapeutic in surgically resected NSCLC. *Melanoma-associated antigen 3* (*MAGE-A3*) is a human gene that encodes a tumor-specific antigen (MAGE-A3 protein) expressed in 30–50% of NSCLC particularly in squamous-cells carcinomas. This gene is silent in all normal human tissue except in placenta and testis. MAGE-A3 immunotherapeutic includes recombinant MAGE-A3 protein given with an immune-stimulant. Patients enrolled in the MAGRIT trial had a histologically proven, completely resected stage IB, II or IIIA MAGE-A3 expressing NSCLC evaluated with quantitative polymerase chain reaction (PCR). Patients were randomized 2:1 between October 2007 and July 2012 to receive 13 intramuscular injections of MAGE-A3 (n=1,515) or placebo (n=757). In the overall population, median disease-free survival was 60.5 months for the MAGE-A3 immunotherapeutic group and 57.9 months for the placebo group [hazard ratio (HR): 1.02; 95% CI: 0.89–1.18; P=0.74]. Among patients who did not receive chemotherapy, median disease-free survival was 58.0 months in the MAGE-A3 group and 56.9 months in the placebo group (HR: 0.97; 95% CI: 0.80–1.18; P=0.76). These data demonstrated that MAGE-A3 immunotherapy is not effective in patient with surgically resected early NSCLC. Therefore, further development of MAGE-A3 immunotherapeutic for use in NSCLC has been abandoned (6).

The MAGRIT trial is not the only negative vaccination trial. Another two studies (START trial and STOP trial), assessing therapeutic vaccinations, failed in proving efficacy in treatment of NSCLC and did not reach their primary endpoint (5,7).

The phase 3 Stimulating Targeted Antigenic Responses to NSCLC (START) trial recruited patients with unresectable stage IIIA and IIIB NSCLC with stable or objective response after concurrent or sequential chemoradiotherapy. Patients were randomly assigned (2:1, double blind) to either tacemotide or placebo given every week for 8 weeks and then every 6 weeks until disease progression or

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withdrawal. Tacemotide is a mucin 1 glycoprotein (MUC1) antigen specific immunotherapy able to induce a T-cell response to MUC1 in preclinical lung cancer mouse model and in patients. MUC1 is overexpressed and glycosilated in NSCLC. MUC1 is involved in interactions with receptor tyrosine kinases and other cell surface receptors. These abnormal interactions result in inappropriate activation of intracellular pathways promoting growth, proliferation and survival of cancer cells. No significant difference in OS was observed with tacemotide after chemoradiotherapy compared with placebo. Patients who received concurrent chemoradiotherapy revealed a 10-month improvement in median OS, but further investigation (phase III START2 trial) was stopped (8).

Belagenpumatucel-L is an allogenic whole tumour cell vaccine of four NSCLC cells lines transfected with transforming growth factor β (TGF-β2) antisense vector. These cells were grown in cultures and were irradiated. TGF-β2 is involved in immunosuppressive environment of NSCLC. Survival: tumor-free, overall and progression-free (STOP) trial was a phase III, randomized, double blind trial, designed to assess the efficacy of belagenpumatucel-L1 as maintenance therapy in stage III/IV NSCLC patients who did not progress after first line platinum-based chemotherapy. Patients were randomly assigned (1:1) to receive belagenpumatucel-L1 or placebo monthly during 18 months and at 21 and 24 months. The primary endpoint of OS did not differ between the two arms. Although a subgroup analysis showed a significant benefit in median OS in patients who received prior radiation therapy, the very low number of patients precludes any firm conclusion (9).

An open-label phase 2B trial evaluated the effect of TG4010 in combination with first-line chemotherapy in advanced NSCLC. TG4010 is a suspension of recombinant modified poxvirus that code for MUC1 antigen and IL-2. Patients with IIIB/IV NSCLC expressing MUC1 by immunohistochemistry were enrolled in parallel groups to receive TG4010 plus cisplatin and gemcitabine every 3 weeks for up to six cycles or the same chemotherapy alone. There was no significant difference in OS (10).

More recently, a large meta-analysis on 4,484 patients included in 17 randomized clinical trials showed that immunotherapy extended survival and progression-free-survival (PFS). Interestingly, there was a benefit of immunotherapy in low stage over high stage NSCLC in terms of survival (11).

Data from MAGRIT trial and other studies raise the question on the real role of immunotherapy in the treatment of lung cancer. It is now clear that checkpoint inhibitors are effective in metastatic disease. Recent data showed that nivolumab (12,13), pembrolizumab (14) and atezolizumab (15) are superior to docetaxel in second-line setting and pembrolizumab (14) also improve survival versus platinum-based chemotherapy in PD-L1 positive untreated NSCLC. The efficacy of checkpoint inhibitors in the adjuvant setting is under investigation and at the present time such agents are not recommended in early stage NSCLC. Data from checkpoint inhibitor trials clearly indicated that such agents are not effective in all NSCLC and currently available biomarkers, specifically PD-L1 expression, are weak predictors for immunotherapy efficacy (12,13). The lack of selection could be one of the most relevant reasons of MAGRIT trial failure. Recent data suggested that immunotherapy could result more effective against tumors with high neoantigen burden (16). In addition, although patients were selected for MAGE-A3 expression, the normal function of MAGE-A3 is unknown, monovalent molecularly defined vaccines might be too weak to make an impact, metastatic or progressive tumours may be immune escape variants. Therefore, the future opportunities for vaccines in NSCLC could be personalized molecular vaccines based on mutanome analysis and autologous whole tumour antigen vaccines designed to address specific mutations.

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