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MAGE-A3-specific anticancer immunotherapy in the clinical practice

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Antigen-specific immunotherapy may offer a unique approach to fight cancer. We have demonstrated that specific immunotherapeutic regimens involving recombinant melanoma antigen family A3 (MAGE-A3) and different immunostimulants exert clinical anticancer activity. In particular, the combination of recombinant MAGE-A3 and AS15, a multicomponent immunostimulant, was found to elicit robust antigen-specific immune responses.

Over the past decades it has been amply demonstrated that cancer cells can be recognized (and in selected circumstances even eliminated) by the host immune system. The tumor-associated antigen (TAA) melanoma antigen family A3 (MAGE-A3) was the first human TAA found to be specifically recognized by $CD8^+$ T cells. MAGE-A3 is expressed by a wide variety of neoplasms but not by normal tissues, exception made for testes and placenta.[1] However, in these tissues, MAGE-A3-expressing cells cannot present it to $CD4^+$ and $CD8^+$ T lymphocytes. Consequently, MAGE-A3 is considered as a promising TAA for the selective targeting of malignant cells with immunotherapy.

In 2 recent Phase II clinical studies, we used antigen-specific immunotherapy to generate immune responses against MAGE-A3. Our aim was to activate host immune effectors to eradicate MAGE-A3-expressing tumors.

The first study was performed in 182 patients with completely resected non-small cell lung carcinoma (NSCLC).[2] The primary objective of this study was the evaluation of the disease-free interval (DFI). After a median follow-up period of 44 mo, recurrence was observed in 35% of patients receiving a recombinant MAGE-A3-based vaccine (n = 122) and in 43% of patients allocated to the placebo arm of the study (n = 60). In this setting, a trend in support of the capacity of MAGE-A3-based immunotherapy to provide clinical benefits to NSCLC patients was observed, but the small size of the cohort prevented statistically significant differences from openly manifesting.

The second study evaluated the clinical activity of MAGE-A3-based immunotherapy in metastatic melanoma patients. In this case, recombinant MAGE-A3 was administered in combination with 2 distinct immunostimulants, $AS02_B$ and AS15.[3] Both these immunotherapeutic regimens had an acceptable safety profile, with no immunological adverse events (AEs) reported. Conversely, progression-free survival (PFS) rates (19% vs. 3%) and OS (33 vs. 19 mo) were significantly improved among patients receiving MAGE-A3 together with AS15 rather than in combination with $AS02_B$.

In both studies, patients receiving MAGE-A3-based immunotherapy developed MAGE-A3-specific antibodies. In addition, in the second study, humoral and $CD4^+$ T-cell responses were more pronounced in patients receiving recombinant MAGE-A3 plus AS15 that among patients treated with recombinant MAGE-A3 plus $AS02_B$. Of note, $CD8^+$ T-cell responses specific for MAGE-A3 were rare in both arms of this study, as only 1 patient receiving MAGE-A3-based immunotherapy in combination with AS15 could be considered as a responder.

We also investigated whether a specific gene signature (GS) would predict clinical responses to MAGE-A3-based anticancer immunotherapy.[4] Using tumor biopsies obtained before immunization, we observed that the expression of 84 genes with immune functions correlated with the response of melanoma patients to immunotherapy (**Fig. 1**). The influence of this GS on OS was more robust when recombinant MAGE-A3 was given in combination with AS15 than when it was combined with $AS02_B$ (**Fig. 1A**). The same GS was then used to seek any correlation with clinical outcome in NSCLC patients. Indeed, patients bearing GS-positive NSCLCs and receiving MAGE-A3-based immunotherapy exhibited a favorable DFI when compared with similar patients treated with placebo. Conversely, no difference was observed between the DFI of individuals bearing GS-negative tumors receiving MAGE-A3-based immunotherapy or placebo (**Fig. 1B**). Additionally, a difference in OS was observed when patients were stratified according to GS status (**Fig. 1C**). These results, which have been obtained on a reduced number of cases, are awaiting prospective validation.

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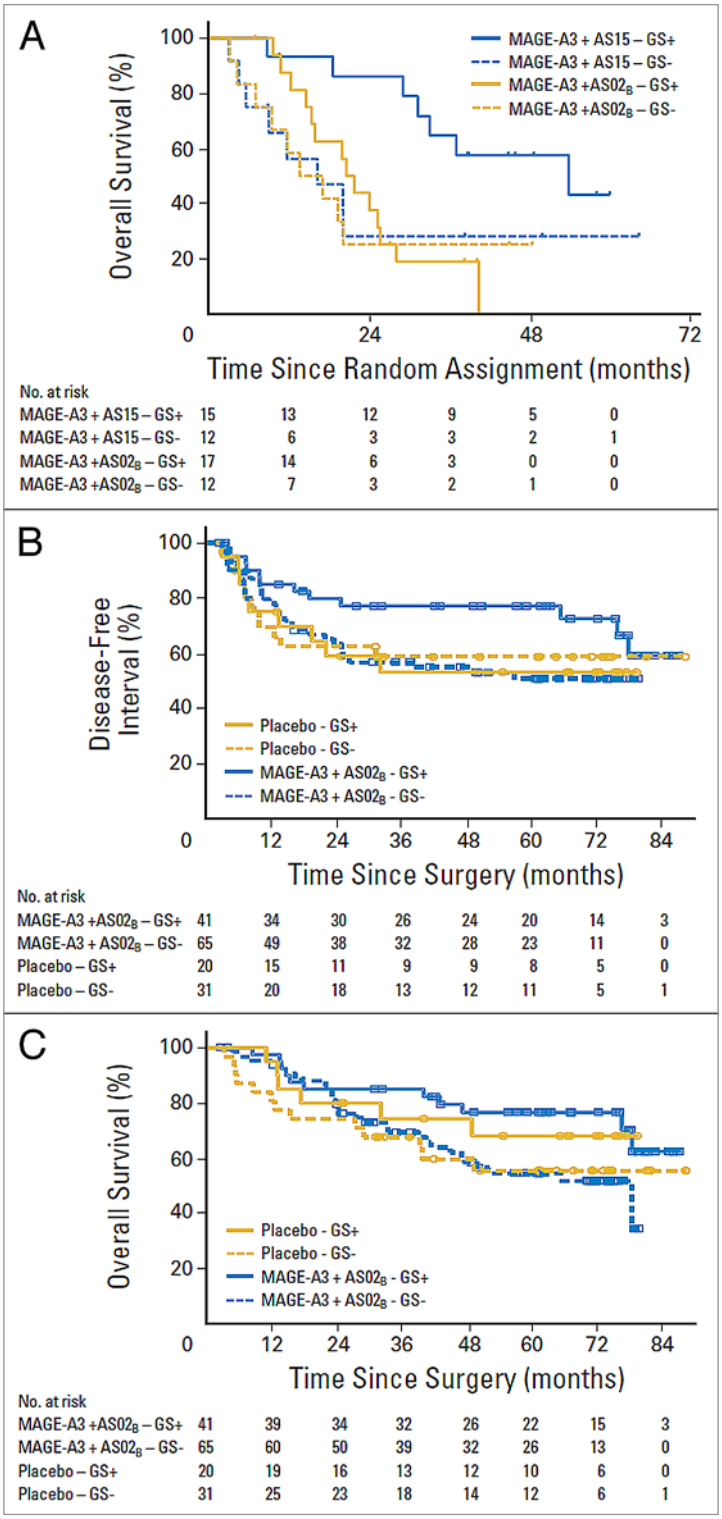

Figure 1. Clinical impact of MAGE-A3-based anticancer immunotherapy. (**A**) Overall survival (OS) of metastatic melanoma patients stratified according to treatment (recombinant MAGE-A3 plus AS15 or $AS02_B$) and gene expression signature (GS) status. Hazard ratios (HRs) between the GS+ and GS- populations were 0.37 (95% CI, 0.13 to 1.05; p = 0.06) in the AS15 arm and 0.84 (95% CI, 0.36 to 1.97; p = 0.70) in $AS02_B$ arm. Results are from a 4-y median observation period. As a reference, the HRs between the AS15 and $AS02_B$ arms were 0.48 (95% CI, 0.24 to 0.94) in the patient population analyzed for GS and 0.56 (95% CI, 0.31 to 0.98) in the entire study population. (**B**) Disease-free interval (DFI) of non-small cell lung carcinoma (NSCLC) patients (adjuvant setting) stratified according to treatment (recombinant MAGE-A3 + $AS02_B$ or placebo) and GS status. HRs between individuals receiving active immunotherapy or placebo were 0.42 (95% CI, 0.17 to 1.03; p = 0.06) for 61 GS+ patients and 1.17 (95% CI, 0.59 to 2.31; p = 0.65) for 96 GS- patients. As a reference, the HRs between subjects treated with active immunotherapy and placebo-treated patients were 0.85 (95% CI, 0.50 to 1.43) in 157 patients analyzed for GS and 0.78 (95% CI, 0.49 to 1.24) in the entire study population (including 182 patients). Figure legend continued on e25995-3.

Figure 1 (Continued). HRs between the GS+ and GS- patient populations were 1.23 (95% CI, 0.51 to 2.98; p = 0.65) for the 51 patients of the placebo arm and 0.44 (95% CI, 0.22 to 0.88; p = 0.02) for the 106 actively treated patients. Results are from a median 70-mo observation period. Results from an early (44-mo) analysis were qualitatively similar. (**C**) OS (median 70-mo observation period) of NSCLC patients (adjuvant setting) stratified according to treatment (recombinant MAGE-A3 + $AS02_B$ or placebo) and GS status. HRs between subjects treated with active immunotherapy and placebo-treated individuals were 0.63 (95% CI, 0.22 to 1.78; p = 0.38) for 61 GS+ patients and 1.09 (95% CI, 0.56 to 2.11; p = 0.81) for 96 GS- patients. As a reference, the HRs between subjects treated with active immunotherapy and placebo-treated patients were 0.93 (95% CI, 0.54 to 1.61) for the 157 patients analyzed for GS and 0.99 (95% CI, 0.60 to 1.64) in the entire study population (182 patients). HRs between the GS+ and GS- patient populations were 0.69 (95% CI, 0.25 to 1.86; p = 0.46) for the 51 patients of the placebo arm and 0.39 (95% CI, 0.19 to 0.81; p = 0.01) for the 106 actively treated patients. In **B** and **C**, open circles and open squares indicate censored patients. Figure is reproduced with permissions from Ulloa-Montoya et al.[9]

To date, different immunotherapeutic regimens have been investigated for their ability to mediate clinically relevant antineoplastic effects. Non antigen-specific immunotherapeutic interventions, such as the blockade of immunosuppressive receptors like cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD-1), have shown promising results in patients affected by metastatic melanoma and other tumor types. Along similar lines, promising response rates have been reported upon the administration of monoclonal antibodies targeting PD-1 or its main ligand (PD-1L) to NSCLC and renal cell carcinoma patients, including some durable responses.[5,6] However, the elicitation of immunological AEs may remain an issue for the development of adjuvant therapies based on these immunotherapeutic agents.

More recently, T cells expressing an affinity-enhanced MAGE-A3-specific T-cell receptor (TCR) have been shown to exert clinical activity. However, serious side effects were also reported, which presumably originated from the supraphysiological avidity of TCR-engineered T-cells, promoting cross-reactivity with off-target antigens.[7]

Our approach was to use TAA-specific immunotherapy to generate immune responses against MAGE-A3. MAGE-A3-based anticancer immunotherapy demonstrated clinical activity in 2 distinct clinical settings, namely, among resected NSCLC and metastatic melanoma patients. In particular, the combination of recombinant MAGE-A3 with the multicomponent immunostimulant AS15 appeared to exert superior antineoplastic activity. The key role of immunostimulants in humoral and cellular immune responses induced by MAGE-A3-based immunotherapy, as well as in its clinical activity, had previously been demonstrated. The administration of recombinant MAGE-A3 alone fails indeed to trigger antitumor immunity.[8]

Overall, MAGE-A3-based anticancer immunotherapy appears to have interesting features, i.e., to presumably be tumor-specific and capable of inducing long-lasting TAA-specific memory T lymphocytes in patients. The downside of this approach resides in its single antigen-specificity and in the modest immunogenicity of MAGE-A3 when compared with mutated TAAs or neo-antigens.[9] Nevertheless, the presence in MAGE-A3 of multiple epitopes for presentation to $CD4^+$ and $CD8^+$ T cells, and the use of immunostimulants allowed our immunotherapeutic approach to trigger TAA-specific humoral responses and to exert clinical activity. Importantly, MAGE-A3-based anticancer immunotherapy has been associated with an acceptable safety profile, with no immunological AEs reported so far. Two Phase III studies (NCT00480025, NCT00796445) are currently ongoing to demonstrate the clinical safety and efficacy of recombinant MAGE-A3 combined with AS15. These studies may also allow us to validate the predictive value of the immunological GS that we have recently identified.

Disclosure of Potential Conflicts of Interest

Vincent Brichard is employee by the GlaxoSmithKline group of companies and owns stock options. Quentin Godechal is consultant for GlaxoSmithKline Vaccines

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