Epigenetic immunomodulation by SGI-110 combined with immune check-point blockade as a new therapeutic strategy

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Abstract

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Results

Background: SGI-110 is a dinucleotide of 2'-deoxyguanosine (2'-dG) and 2'-deoxycytidine (2'-dC), which is a potent inhibitor of DNA methyltransferase and has a preferential affinity for tumor suppressor genes, which are usually silenced in cancer cells. Therefore, SGI-110 is a promising candidate for use in cancer therapy. Immunomodulation by SGI-110 has also been demonstrated in various experimental systems. In vivo experiments using an orthotopic tumor xenograft model and clinical trials have shown that SGI-110 can enhance the immune response to cancer antigens and improve the efficacy of immune checkpoint inhibitors. In this study, we evaluated the contribution of anti-tumor immune responses in the reduction of tumor growth achieved by the therapeutic combination of SGI-110 with immune checkpoint blockade.

Materials and Methods: BALB/c mice were SQ grafted, in the flank region, with the poorly immunogenic murine mammary carcinoma TS/A cells (2×10⁵). Then, groups of mice were ip injected with diluent solution for control, 3mg/kg SGI-110, 100μg anti-CTLA-4 mAb or the combination of SGI-110 and anti-CTLA-4 mAb. Tumor volumes (TV) from each group were measured periodically, all along the treatment, by using a caliper and calculated as TV=LD²/2 (in which L is the longest diameter and D the shortest diameter). Tumor weight was measured at necropsy. Immunohistochemical analysis of tumor infiltrating immune cells was also performed. P1A-promoter methylation was tested by quantitative Methylation-Specific PCR (qMSP) on genomic DNA from tumor tissues. Results: The expression of P1A and Mage-a family members was induced in cancer tissues from animals treated with SGI-110, either alone or in combination with anti-CTLA-4 mAb, but not from mice treated with anti-CTLA-4 mAb alone. Levels of P1A-specific mRNA were similar in tumors from mice treated with SGI-110 alone (1.18±0.04) and P1A-β-adin molecules), with the combination of SGI-110 and anti-CTLA-4 mAb (1.8±0.04) and SGI-110 (2±0.02) mice. The hypomethylating effect of SGI-110 was sustained by the reduction of P1A promoter methylation in cancer tissues from SGI-110- (16%) and combination- (7%) treated mice vs control. Epigenetic remodelling was restricted to tumor tissue leaving almost unaltered normal ones. The contribution of immune cells in the therapeutically effective treatment was supported by the increased frequency of tumor infiltrating CD8+ cells in the combination arm (11±1.9) vs control (3±1.4) or single agent, anti-CTLA-4 mAb (3±1.1) and SGI-110 (4±1.7), treated mice.

Conclusion: These data highlight the involvement of the immune system in the anti-tumor effect of SGI-110 combined with CTLA-4 blockade. Based on the experimental evidences, an exploratory phase I trial to evaluate safety and immunobiologic activities of the combination is being activated in advanced melanoma patients.

Fig 2. RT-PCR analysis of murine CTA expression by SGI-110 combined with anti-CTLA-4 mAb

Fig 3. Regulation of P1A expression by SGI-110 combined with anti-CTLA-4 mAb

Conclusions

- SGI-110 treatment induces a positive modulation of CTA-profile in poorly immunogenic tumor grafts, and is sustained by specific promoter demethylation;
- Modulation of CTA expression by SGI-110 is preferentially directed to tumor tissue, without significantly affecting normal tissue;
- The improved anti-tumor activity of SGI-110 combined with anti-CTLA-4 mAb is mediated by cellular immunity;
- Cellular immunity mediated by the combination regimen is preferentially directed to tumor tissue, without significantly affecting normal ones.

The immunomodulatory properties of SGI-110 make it an attractive therapeutic agent to improve the anti-tumor activity of anti-CTLA-4 mAb and to increase the partial therapeutic efficacy of immunomodulatory mAb to poorly immunogenic tumors.

A phase I/II clinical study that will first test SGI-110 isogenic priming followed by CTLA-4 blockade in metastatic cutaneous melanoma patients is planned.

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