AAP China Scholarship Council - CSC 2024 PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : Impact of microbiota on response to anti-BCMA bispecific monoclonal antibodies in patients with multiple myeloma

DIRECTION de THESE

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CO-TUTELLE INTERNATIONALE envisagée : NON

DESCRIPTIF du PRD :

Background & Significance

Microbiota and multiple myeloma

Over the last few years, the understanding of the role of the microbiota in health and disease has rapidly expanded thanks to the possibility of performing a comprehensive metagenomic analysis of the human gut microbiome via evaluation of the bacterial 16S ribosomal RNA (rRNA) gene (1). Perturbation of the gut microbiota, (dysbiosis), has been associated with multiple and varied diseases, including infection, atherosclerosis, inflammatory and metabolic disease, mental illness, neurological disease, and cancer(1). In the field of hematologic malignancy, microbiota research has mainly focused on allogeneic hematopoietic cell transplantation (allo-HCT).
Besides allo-HCT, several studies have recently suggested a role for the microbiota in multiple myeloma (MM). Two studies compared the composition of gut microbiota at diagnosis of MM with healthy controls(10, 11). While few MM patients were included in these studies (19 and 40 respectively), both studies evidenced alteration of gut microbiota composition at diagnosis in MM patients. In particular, one study suggested, using a MM mice model, that nitrogen-recycling bacteria such as *Klebsiella* and *Streptococcus* promote MM progression through production of glutamine(10). Furthermore, another study performed in a mouse myeloma model showed that the microbiota drives IL-17 producing cells and eosinophils that synergize to accelerate myeloma progression(12). Furthermore, in a group of 34 MM patients receiving first-line treatment, a correlation between microbiota composition (higher relative abundance of *Eubacterium hallii*) and achievement of MRD negativity was observed, further supporting a role of the microbiota in MM pathogenesis(13). Finally, Khan *et al*. recently evaluated the impact of microbiota diversity on patient outcome in a large cohort of adult patients undergoing high-dose chemotherapy and autologous hematopoietic cell transplantation (auto-HCT) for MM (14). They found that auto-HCT was associated with decreased fecal microbiota diversity and that patients with a greater degree of microbiome damage (below-median fecal intestinal diversity) at neutrophil engraftment had worse progression-free survival than those with less microbiome damage.(15).

Immunotherapy and microbiota
In addition, impact of microbiota on cancer response after immunotherapy is well established. Therefore, intestinal microbiota richness was found to be associated with a better response to anti PD-1 immunotherapies, namely in non-small cell lung cancer (NSCLC), renal cell carcinoma, urothelial carcinoma(16) and melanoma(17). Furthermore, Smith et al. evaluated the impact of antibiotic and microbiota in a cohort of patients that received anti-CD19 CART cells for B-cell lymphoma or acute lymphoblastic leukemia(18). They found in a retrospective cohort (n = 228) that exposure to antibiotics, in particular piperacillin/tazobactam, meropenem and imipenem/cilastatin (P-I-M), in the 4 weeks before therapy was associated with worse survival and increased neurotoxicity (ICANS). Furthermore, in stool samples from a prospective cohort of CAR T cell recipients (n = 48), they found that fecal microbiome was altered at baseline compared to healthy controls. Stool sample profiling by 16S ribosomal RNA and metagenomic shotgun sequencing revealed that clinical outcomes were associated with differences in specific bacterial taxa and metabolic pathways. In particular, they identified species within the class Clostridia that were associated with day 100 complete response. Overall, changes in the intestinal microbiome are associated with clinical outcomes after anti-CD19 CAR T cell therapy in patients with B cell malignancies.

With this background, the aim of our study is to evaluate the impact of microbiota composition on clinical response and side effects after anti-BCMA bispecific monoclonal antibodies. In

particular we would like to assess the interplay between microbiota composition, effector immune cells and clinical outcomes.

Objective:

- To compare microbiota composition of patients with MM at initiation of bispecific monoclonal antibodies according to response status.
- To compare microbiota composition of patients with MM at initiation of bispecific monoclonal antibodies according to the presence or absence of each side effects (CRS, ICANS, cytopenia and infectious complication…)
- To correlate gut microbiota composition with immune status (PBMC) and patients outcomes at the different time point. Immune status will be evaluated by flow cytometry using CYTOF and a minimum of 50 parameters characterizing conventional and unconventional T cells, Treg, B cells, Dendritic cells, and by scRNAseq analysis.

Innovation

Several reports already evidenced a link between gut microbiota composition and response to treatment in MM patients(13, 14). Furthermore, a mouse model study provides evidence of a role of the microbiota in MM tumoral promotion(12). So far, however, no data exist on the evaluation of the gut microbiota pattern in patients treated with anti-BCMA monoclonal antibodies. Our research project will decipher the gut microbiota pattern and immune status in those patients and the impact on response to treatment and side effects. Therefore, our highly innovative research project may allow us to identify a role of the microbiota in response to treatment. This will offer opportunities to develop the use of microbiota manipulation, and more particularly fecal microbiota transplantation (FMT) as a therapeutic tool for MM patients. The applicant has already carried out several clinical trials evaluating FMT in patients with hematologic malignancies(19), and patients with graft-versus-host disease after allo-HCT(NCT03359980). This offers a strong guarantee that this translational project could quickly translate form the bench to the bedside.

Experimental Approach

Inclusion criteria:

- Any patient with MM that will received anti-BCMA bispecific monoclonal antibodies within around 10 centers over a 1 year period.

Methods

- Stool sampling and PBMC before initiation of anti-BCMA bispecific monoclonal antibodies (D1) and then at D8, D15 and D22 of the first course, at D1 of the course 2, 3 and 4 and then every 3 months until progression or relapse
- Additional stool sampling and PBMC will be collected in case of event of interest: toxicity, progression or relapse
- Cytogenetics, ISS-R, MRD status, will be evaluated according to standard guidelines
- Shotgun microbiome sequencing will be preformed
- Data will be collected through flow-chart review. Particular attention will be paid to the toxicity and the use of antibiotics.

Statistical analysis

Patients' characteristics will be expressed as median (range). Bacterial reads from that study will be analyzed through the DADA2 pipeline. The Wilcoxon rank-sum test will be used to compare alpha diversity between the responder and non-responder or between the different group of interest from the current study with the phyloseq package (version 1.30.0). The top ten overall genus-level taxa will be ranked in each group and compared.

AVIS de l'Ecole Doctorale :

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Fichier à envoyer par mail simultanément
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