COMY CONGRESS
SESSION 6: INNOVATIVE APPROACHES AND CASE DISCUSSIONS
ROLE OF CHECKPOINT INHIBITORS
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Summary of the presentation

The generation of an effective anticancer immunity is a complex multistep process that needs, first the release of cancer cell antigens by the tumor, second the processing and presentation of these antigens by dendritic cells or APC in the context of MHC molecules, third the priming and activations of Tcells, trafficking and infiltration of T cells to tumors, and finally the recognition of the cancer cells by the T cells and its activation and killing of cancer cells. Unfortunately tumors display a wide variety of mechanisms to effectively evade immune control. Among others, the production of cytokines that suppress dendritic and T-cell activation, the down-regulation of MHC class I molecules and the up-regulation of surface ligands such as PD-L1, that mediate T-cell anergy or exhaustion, are important mechanisms displayed by cancer cell to escape immune surveillance. Therefore, we can enhance anticancer immunity in four different ways: 1) direct targeting of surface tumor antigens using monoclonal antibodies; 2) boosting immune effectors with adoptive cell therapy; 3) activating tumor specific immunity with vaccines and 4) overcoming inhibitory immune suppression generated by the tumor with immunomodulatory drugs and checkpoint inhibitors.

The checkpoints are co-stimulatory signals that are needed for the adequate activation of T-cells. In the absence of this second signal T-cells fails to respond and become inactivated. There are two different types of checkpoint receptors: activating receptors (such as CD28, OX40) and inhibitory receptors (PD-1, CTLA4, TIM-3…). Cancer cells use PD-1 and CTLA-4 pathways to create an immunosuppressive milieu and escape immune control. We can use drugs targeting these molecules in order to unmask the cancer cell, make it visible to the immune system and amplify the T-cell response. So far we have different drugs, some already approved, that target checkpoint inhibitory receptors such as CTLA-4 (ipilimumab) or PD-1 (nivolumab, pembrolizumab); they have been investigated in different types of tumors, including hematological malignancies, such as Hodgkin lymphoma, with impressive results, and more recently, in Multiple Myeloma in combination with IMIDs. In a phase I trial the combination of pembrolizumab (anti PD-1) with lenalidomide and dexamethasone has been investigated in 50 heavily-pretreated RRMM patients. The preliminary results in the first 17 patients included in the dose determination/confirmation cohorts has shown an ORR of 76%, and 56% in those patients that were refractory to lenalidomide. Another trial with the same drug (pembrolizumab) but in combination with pomalidomide-dexamethasone, showed similar promising results with a global ORR of 60%, and 55% in patients that were double refractory (to PI and IMID).

Short biography

Dr. Paula Rodríguez-Otero studied medicine at he University of Navarra, Pamplona, Spain. Subsequently she completed her residency training program in hematology at the Clinic of the University of Navarra and became faculty at the department of the same institution. After completing her PhD she focused her clinical interest in the management and biology of allogeneic stem cell transplant, which brought her to perform a clinical fellowship in the bone marrow transplant division at the Hôpital Saint-Louis, in Paris. In 2011 she joined back the Department of Hematology at the University of Navarra, where she has become a member of the Myeloma Unit and leads the clinical trials and immunotherapy program under the direction of Professor Jesus San Miguel.