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Editorial

The Evolution in The Treatment of Multiple Myeloma Towards Targeted Magnetic Molecularly Imprinted Nanomedicines

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Multiple myeloma is the second more frequently haematological cancer in the western world, after non-Hodgkin lymphoma, being about the 1-2 % of all the cancers cases and the 10-13% of hematologic diseases. The disease is caused by an uncontrolled clonal proliferation of plasma cells in the bone marrow that accumulate in different parts of the body, usually in the bone marrow, around some bones, and rarely in other tissues, forming tumor deposits, called *plasmocytomas*. This uncontrolled clonal proliferation of plasma cells produces the secretion of an abnormal monoclonal immunoglobulin (paraprotein or M-protein) and prevents the formation of the other antibodies produced by the normal plasma cells that are destroyed. The anormal secretion of paraproteins unbalance the osteoblastosis and osteoclastosis processes, leading to bone lesions that cause lytic bone deposits and the release of calcium from bones (hypercalcemia) that may produce renal failure. Regions affected by bone lesions are the skull, spine, ribs, sternum, pelvis and bones that form part of the shoulders and hips. The substitution of the healthy bone marrow by infiltrating malignant cells and the inhibition of the normal production of red blood cells produce anaemia, thrombocytopenia and leukopenia. Multiple myeloma patients are immunosuppressed because of leukopenia and the abnormal immunoglobulin production caused by the uncontrolled clonal proliferation of plasma cells, being susceptible to bacterial infections, like pneumonias and urinary tract infections. The interaction of immunoglobulin with hemostatic mechanisms may lead to haemorrhagic diathesis or thrombosis. Also, disorders of the central and peripheral nervous system are part of the disease, being the more common neurological manifestations the spinal cord compressions and the peripheral neuropathies.

The treatment of multiple myeloma has been a real headache for a long time since the disease is relatively resistant to traditional chemotherapy because the majority of plasma cells do not divide, limiting the effectiveness of conventional cytotoxic agents that affect overall to rapidly growing cells. However, since the early 1980s the treatment of multiple myeloma has evolved from the death after about two years of progressive deterioration of quality of life, until more and more large asymptomatic periods of complete remission by more advanced and targeted therapies like the high-dose therapies supplemented with autologous stem-cell transplantation, and the use of novel molecular-targeted agents (immunomodulatory drugs and proteasome inhibitors), achieving survivals of more than ten years in some patients that continue with their first complete remission. Note that the complete remission state is an important prognostic factor for survival in myeloma patients and can be defined as an absence of monoclonal paraprotein in serum and urine, less than five percent of plasma cells in bone marrow, no increase of lytic bone lesions, and disappearance of plasmacytomas.

The current treatment of multiple myeloma comprises supportive treatment and initial induction chemotherapy courses, followed by single or double high dose therapy supported with autologous transplant, and finished by a consolidation therapy that prolongs significantly the survival of patients. Although the treatment with alkylating compounds, like melphalan, bendamustine and cyclophosphamide, and corticosterioids have been the traditional chemotherapeutic cocktail for the treatment of multiple myeloma for decades, the understanding of the biology of multiple myeloma has allowed the development of *novel biological agents* that target myeloma cells and the bone-marrow microenvironment, which has a fundamental role in multiple myeloma pathogenesis. Note that survival of malignant myeloma cells is dependent on the bone

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marrow microenvironment and the evasion of the anti-tumor immune responses. Among these new agents should be noted the immunomodulatory drugs (IMiDs), like thalidomide and derivatives (lenalidomide and pomalidomide) and the proteasome inhibitors drugs, like bertezomib and carfilzomib (and several new agents in phase II and III trials, like marizomib, ixazomib and oprozomib). Although, the incorporation of IMiDs and proteasome inhibitors in the treatment of multiple myeloma has improved long-term outcome of patients, increasing their overall survival, many patients relapsed or were refractory to these drugs because of myeloma cells increase the secretion of survival factors and become unaffected to apoptotic signals, dying as a result of disease or complications arising. Therefore, there are novel agents under preclinical and clinical investigation, like histone deacetylase inhibitors (vorinostat, panobinostat, belinostat y romidepsina), heat shock protein 90 inhibitors, arsenic trioxide, deubiquitylating enzymes inhibitors, monoclonal antibodies (elotuzumab, daratumumab, lorvotuzumab, siltuximab, tabalumab, denosumab, figitumumab, bavacizumab, mapatumumab, dacetuzumab, lucatumumab and milatuzumab, among others), and inhibitors of different signaling pathways, that explore new mechanisms to interfere with the interactions between the malignant plasma cells and its microenvironment, achieving promising results in the fight against relapsed/refractory multiple myeloma. However, despite all efforts, multiple myeloma has no cure nowadays.

To provide a step forward in the treatment of multiple myeloma, the use of targeted magnetic molecularly imprinted nanomedicines may avoid the traditional treatments of this pathogenesis that involve a large deterioration in the quality of life of the patients for long periods and are not always effective. These novel magnetic nanomedicines will be able to remotely destroy the plasma cells and prevent the cancer from coming back again, attacking the bone-marrow microenvironment, decreasing relapse or recurrence and resistance to available drugs.

Although exist a clear rationale for using magnetic hyperthermia (procedure that use heat to kill cancerous cells with minimal damage to normal cells) in haematological cancer treatment, it has been mainly used as adjunctive therapy with radiotherapy and chemotherapy in solid tumors. In literature, there are numerous examples of *in vivo* aplications of magnetic hyperthermia in the treatment of solid tumors, but there are only several papers related to magnetic hyperthermia in hematologic cancers. Nowadays, the more promising approach to generate a locally targeted hyperthermia is the intracellular hyperthermia by means of intravenous administered nano-scale magnetic particles that can generate heat, in the malignant cells of tumors, under a high frequency alternating magnetic field (AMF) by magnetic hysteresis loss for ferro- and ferri-magnetic materials, or Brownian and mostly Neel relaxation pathways for superparamagnetic materials. Note that magnetic hyperthermia based on magnetic nanoparticles received regulatory approval as a new clinical cancer therapy, the thermotherapy, in 2010.

Molecular imprinting

Molecular imprinting is a promising technology that creates *"intelligent materials"* that simulates the typical molecular recognition of biological systems. Molecular imprinting polymers (MIPs) are cross-linked polymeric networks formed in the presence of a template that creates a recognition site. The subsequent release of the template allows the material to exhibit a selective "memory" with respect to the template. This technology has been widely used to recognize small molecules, like herbicides, metal ions or amino acids, in several applications, such us chromatography, sensor technology, separation processes and immunosorbent assays (ELISA). However, researchers have faced many difficulties in recognizing large molecular weight molecules, like peptides and proteins.