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Multiple myeloma: Monoclonal antibodies-based immunotherapeutic strategies and targeted radiotherapy

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ABSTRACT

Multiple myeloma (MM) is an incurable B-cell malignancy of terminally differentiated plasma cells. Besides conventional treatments, several targeted therapies are emerging for MM. We review recent developments in monoclonal antibodies (MoAbs) and (radio)immunoconjugates-based targeted immunotherapeutic (serotherapies) strategies, as well as skeletal targeted radiotherapy (STR™) in MM. MoAbs-based strategies include the targeting of cytokines and their receptors as well as toxins, drugs or radionuclide delivery to MM cells. Both targeted radioimmunotherapy (RIT) and STR™ have proved efficient in the treatment of radiosensitive tumours. We conclude that there is a need for more mechanistic investigations of drug action to identify novel therapeutic targets in myeloma cells, as well as in the bone marrow microenvironment.

1. Introduction

Multiple myeloma (MM) is a haematologic malignancy associated with a variety of clinical manifestations, including osteolytic lesions due to uncoupled bone metabolism, anaemia and immunosuppression due to loss of normal haematopoietic stem cell function, and end-organ damage due to monoclonal immunoglobulin secretion.[1] In the United States, the diagnosis of MM involves 15 000 new patients per year with a median expectation of life of 3–4 years. Despite this MM remains incurable, while recent advances in basic biology have led to important insights into its pathophysiology, which in turn are rapidly changing the management and therapeutic strategy of this malignancy. Novel agents, such as thalidomide, lenalidomide and bortezomib, have recently demonstrated an increasing therapeutic role in the treatment of MM patients.[2] However, MM can relapse even after complete remission and therefore new drugs and therapeutic strategies are urgently needed. Here we will review the potential of immunotherapeutic and targeted radiotherapy strategies for treating MM.

2. Therapeutic strategies in MM

2.1. *Immunotherapy*

Immunotherapy is an experimental treatment strategy for MM.[3–7] Strategies to harness the powerful immune system are mainly at the pre-clinical stage of development for MM, but they are moving towards clinical testing. There is wide variety in the techniques used and the outcomes achieved so far. MM patients do not mount a strong immune response

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against their disease. The goal of using immunotherapy is to either help the body elicit an "active" immune response to attack myeloma cells (active immunotherapy) or to substitute an alternative "passive" response elicited outside the body and administered to the patient (passive immunotherapy).[3,6,7] Immunotherapy is likely to be most effective when the burden of disease has been minimized, such as after high-dose chemotherapy and stem cell transplantation (SCT). It seeks to destroy the remaining cells, which are thought to be responsible for relapse after therapy. However, immunotherapy may also have other indirect anti-MM effects,[7] such as: 1) slowing MM cell growth; 2) making MM cells more vulnerable to destruction by other therapies; or 3) affecting the bone marrow (BM) microenvironment to make it less hospitable to MM cells.

Immunotherapy is an active area of research in MM. In addition to monoclonal antibodies (MoAbs), other types of immunotherapy being investigated in MM include vaccines, cytokines as well as manipulation of immune cells. Researchers are investigating new molecular targets and strategies for immunotherapy, as well as working toward a better understanding of the immune defects present in patients with MM.[6–9] (Table 1) The following section deals with various types of MoAb-based strategies under investigation in MM.

2.1.1. *Monoclonal antibodies*

MoAbs target specific molecules and are used as passive immunotherapy to treat various diseases, including certain types of cancer.[3,7] These MoAbs selectively target tumour tissues and have been safely administered in cancer patients.[7] The recent approvals of MoAbs for clinical use[7,9–12] have renewed interest in MoAb-based targeted serotherapies in MM.

Several MoAbs directed against marker proteins expressed on MM cells are being investigated as potential therapeutic tools for MM. MRA (humanized anti-interleukin-6 (IL-6) antibody, atlizumab) is being evaluated in an open-label phase I and II trials to assess the safety and efficacy in MM. Blockade of IL-6R may prove effective in limiting MM cell growth. It is given as monotherapy to patients with MM who are not candidates for, or who have relapsed after SCT.[7,9] The TRM-1 (Fully Human TRAIL-R1 MoAb) is directed against a specific receptor on MM cells known as TRAIL (TNF-related apoptosis-inducing ligand). Binding of the MoAb to TRAIL contributes to MM cell death. TRM-1 is being evaluated in a phase I, open-label, dose-escalation trial to assess the safety, tolerability, immunogenicity, and pharmacokinetics in subjects with MM.[7] The AHM (anti-HM1.24 MoAb) is presently in phase I clinical trials. HM1.24 is a marker expressed on MM cells. MoAbs to HM1.24 have been shown to induce killing of MM cells *in vitro* and *in vivo*.[7] The mKap is a murine MoAb that is specific for free human kappa light chains (the small arms of antibody molecules) and a marker on the surface of plasma cells (PCs). This antibody induces apoptosis in MM cell lines that express the surface antigen KMA *in vitro* and exhibited antitumour activity in a mouse model of disease. Complete data of the preclinical animal trials are expected by late 2005–06.[7,9] The SGN-40 (anti-huCD40 MoAb) is a humanized anti-CD40 MoAb directed against the CD40 receptor on MM cells. Currently, it is being investigated in a phase I, multi-dose trial in patients with refractory or recurrent MM.[7,9] Anderson and co-workers[13] examined the potential therapeutic utility of SGN-40 for treating human MM using MM cell lines and patient MM cells ($CD138^{++}$, $CD40^{+}$). Results showed that, SGN-40 induced modest cytotoxicity, and in the presence of *de novo* protein synthesis inhibitor cycloheximide, it significantly induced apoptosis in dexamethasone (Dex)-sensitive and Dex-resistant MM cells and in patient MM cells. Pretreatment of MM cells with SGN-40 blocked sCD40L-mediated phosphatidylinositol 3′-kinase/akt and nuclear factor-$\kappa\beta$ activation. Moreover, SGN-40 suppressed IL-6R expression at mRNA and protein levels, and importantly, pretreatment of MM cells with SGN-40 inhibited proliferation triggered by IL-6 but not by insulin-like growth factor-1 (IGF-1). SGN-40 has direct anti-MM effects that are unrelated to antibody-dependent cell cytotoxicity (ADCC), highlighting the preclinical rationale for the evaluation of SGN-40 as a potential new therapy. A recent similar study focused on the efficacy of a fully human anti-CD40 MoAb, CHIR-12.12 against human MM cells.[14] CHIR-12.12 triggered lysis of MM cells via ADCC, but did not induce ADCC against CD40-negative MM cells, confirming specificity against CD40-expressing MM cells. The study thus provides the preclinical rationale for clinical trials of CHIR-12.12 in MM.

2.1.1.1. Targeted Anti-IL-6 MoAb therapy. Experimental and clinical findings support the role of IL-6 in cancer and provide a rationale for targeted therapeutic investigations. Various therapeutic agents affect IL-6-mediated effects. Known inhibitors of IL-6 include corticosteroids, non-steroidal anti-inflammatory agents, estrogens, and cytokines (e.g., IL-4).[15] Dex has also been shown to inhibit both IL-6 and IL-6R gene expression in MM cell lines. Targeted biological therapies include IL-6-conjugated MoAbs directed against IL-6 and IL-6R.[15,16] Initial investigations were conducted with mouse MoAb to IL-6 (murine MoAbs BE-4 and BE-8).[17,18] A patient with primary plasma cell leukaemia (PCL) that was resistant to chemotherapy was the first reported recipient of anti-IL-6.[19] There was inhibition of MM proliferation in the BM, along with decreased serum levels of calcium and monoclonal IgG. Levels of C-reactive protein (CRP) became undetectable and no serious side-effects were noted. This study demonstrated the potential of MoAb therapy against IL-6, resulting in a transient tumour cytostasis and reduction in toxicities from IL-6.[16] A subsequent study by Bataille[18] reported the results of MoAb targeting to IL-6 in MM patients with advanced and progressive MM. More recently, a chimeric mouse MoAb to IL-6 (human-mouse cMoAb to IL-6) with the investigational name CNTO 328 was used in a phase I clinical trial in patients with MM.[20,21] van Zaanen[20,21] conducted a phase I/II study based on a dose-escalation analysis of intravenous (i.v.) infusions of murine-human chimeric (cMoAb) CNTO 328 (CCLB8; now called CNTO 328) in patients with end-stage, progressive MM[22] resistant to second-line chemotherapy. Data from the study enabled the development of a method for calculating endogenous IL-6 production and the finding that CNTO 328 therapy normalized endogenous IL-6 production but did not affect the IL-6 production associated with infection. These investigations suggested that CNTO 328 had a low immunogenicity and was able to block IL-6-dependent processes *in vivo*.[20] In a second report,[21] three additional patients were enrolled in the dose-escalation study and received CNTO 328 as before. The dosing regimen was 40 mg/day in these patients. Disease stabilized in 11 of 12 patients;