Bone 77 (2015) 57–68

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review

A review of current murine models of multiple myeloma used to assess the efficacy of therapeutic agents on tumour growth and bone disease

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ARTICLE INFO

Article history:
Received 25 September 2014
Revised 27 March 2015
Accepted 2 April 2015
Available online 11 April 2015

Edited by: R. Baron

Keywords:
Multiple myeloma
Tumour burden
Bone disease
Murine models

ABSTRACT

Pre-clinical *in vivo* models of multiple myeloma are essential tools for investigating the pathophysiology of multiple myeloma and for testing new therapeutic agents and strategies prior to their potential use in clinical trials. Over the last five decades, several different types of murine models of multiple myeloma have been developed ranging from immunocompetent syngeneic models, e.g. the 5T series of myeloma cells, to immunocompromised models including the SCID xenograft models, which use human myeloma cell lines or patient-derived cells. Other models include hybrid models featuring the implantation of SCID mice with bone chips (SCID-hu or SCID-rab) or 3-D bone scaffolds (SCID-synth-hu), and mice that have been genetically engineered to develop myeloma. Bearing in mind the differences in these models, it is not surprising that they reflect to varying degrees different aspects of myeloma. Here we review the past and present murine models of myeloma, with particular emphasis on their advantages and limitations, characteristics, and their use in testing therapeutic agents to treat myeloma tumour burden and bone disease.

Contents

Abbreviations: BCL-XL, Myc/B cell extra-large; b.i, bone implant; BM, bone marrow; BMD, bone mineral density; Bort, bortezomib; β2M, β2Microglobulin; Car, carfilzomib; CP, cyclophosphamide; Dex, dexamethasone; DKK1, Dickkopf-1; Dox, doxorubicin; GFP, green fluorescent protein; GM-CSF, granulocyte macrophage colony-stimulating factor; HDAC, histone deacetylase; HLA, human leucocyte antigen; Iban, ibandronate; i.c, intracardiac; IFN-α, interferon-α; IGF-1, insulin-like growth factor-1; IL-2, interleukin-2; i.o, intraosseous; i.p, intraperitoneal; i.t, intratibial; i.v, intravenous; Luc, luciferase; MC, myeloma cell; Melph, melphalan; MGUS, monoclonal gammopathy of undetermined significance; MIP1-α, macrophage inflammatory protein-α; MM, multiple myeloma; MOP, mineral oil-induced plasmacytoma; MSC, mesenchymal stem cell; MVD, microvessel density; NK, natural killer; NOD/SCID, non-obese diabetic severe combined immunodeficient; NSG, NOD/SCID-gamma; OPG, osteoprotegerin; Opro, oprozomib; Pam, pamidronate; PCLS, poly-ε-caprolactone polymeric scaffold; RANKL, receptor activator of nuclear factor κ B ligand; s.c, subcutaneous; SCID, severe combined immunodeficient; SDF-1, stromal cell-derived factor-1; shuIL6R, soluble human IL-6 receptor; VCAM, vasculature cell adhesion molecule; XBP-1, X-box binding protein-1; Zol, zoledronic acid; ^{51}Cr, ^{51}Chromium.

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http://dx.doi.org/10.1016/j.bone.2015.04.004
8756-3282/

Introduction

Multiple myeloma (MM) is a B cell neoplasm caused by the expansion of malignant plasma cells in the bone marrow (BM). Typical clinical features of the disease include paraproteinaemia, renal impairment, progressive BM failure, and the development of characteristic lytic bone disease featuring osteoporosis, focal lytic lesions, pathological fractures and hypercalcaemia [1]. The development of new drugs to target both tumour burden and bone disease in MM is heavily reliant upon pre-clinical testing using *in vivo* biological systems, given the limitations of *in vitro* techniques alone. Over the last five decades, several different murine models of MM have been developed, which include xenograft models using human MM cells (MCs) and different strains of severe combined immunodeficient (SCID) mice, in addition to transgenic or syngeneic models that develop murine MM in immunocompetent mice. Here we review past and present murine models of MM, with particular emphasis on their use as pre-clinical tools to assess the efficacy of therapeutics for the treatment of tumour burden and tumour-induced bone disease in MM.

Xenograft models of multiple myeloma in immunodeficient mice

SCID & NOD/SCID models of multiple myeloma

SCID and non-obese diabetic/SCID (NOD/SCID) mice have previously been utilised to test the efficacy of different therapeutics in a variety of different systems, including MM. Both strains lack functional B and T lymphocytes and NOD/SCID mice also have no circulating complement and have low natural killer (NK) cell function [2], which is thought to enhance tumour engraftment. A variety of different MC lines including ARH-77 [3–5], RPMI-8226 [6–9], U266 [9,10], KMS-11 [11], KMS-12-BM [12] and MM.1S [8,13–16], as well as primary patient-derived MCs [17], have been administered to SCID and NOD/SCID mice via various routes (summarised in Table 1).

Features of SCID & NOD/SCID inoculated mice

Subcutaneous (s.c) injection of ARH-77 [4] or RPMI-8266 [8] MCs into SCID mice resulted in tumour growth at the sight of injection, with no disseminated tumour growth. By contrast, when ARH-77 MCs were injected intravenously (i.v) via the tail vein, tumour growth was observed in the BM, kidneys, lungs, liver and brain, in addition to the presence of paraprotein in the serum (IgG κ), osteolytic lesions and paraplegia [4]. This was similar to the results observed when RPMI-8226 cells expressing green fluorescent protein (GFP) were injected i.v into NOD/SCID mice, where paraplegia and tumour dissemination to various sites, including the lungs, liver, kidneys, spleen and bones (displaying lytic lesions), were apparent [7]. Whole body luminescence has also been used to visualise tumour in NOD/SCID or SCID beige mice using MM.1S-GFP-Luciferase (Luc) cells administered i.v. In these models MCs disseminated to various sites within the mice; however, the exact sites were not determined due to the sensitivity of the technique [8,13,15]. In contrast, KMS-12-BM cells injected i.v into

Table 1
A summary of cell types, cell numbers, inoculation routes and treatments tested in the SCID and NOD/SCID models of MM.

Cell type	Cell number	Route of injection	Approx. latency (Days)	Radiation (Rads)	Disease features	Treatments tested	References
ARH-77	1×10^7	s.c	21	150	Tumour growth at site of injection		[4]
	$0.1–10 \times 10^6$	i.v	25–33	150–400	Tumour dissemination, paraprotein, paraplegia, bone disease	Iban	[3,4]
	1×10^6	i.c	40	250	Paraplegia, bone disease	OPG transduced ARH-77 cells	[5]
RPMI-8226	$1–3 \times 10^7$	s.c	N/D	300	Tumour at injection site	Melph, bort, anti-IGF, K-7174 proteosome inhibitor	[8,9]
RPMI-8226-GFP	$2.5–5 \times 10^6$	i.v	21–42	125–300	Tumour dissemination, paraprotein, paraplegia, bone disease	Reovirus	[6,7]
KMS-11	0.5×10^6	i.v	35	N/D	Tumour dissemination, paraplegia, paraprotein		[11]
KMS-12-BM	1×10^6	i.v	35–84	N/D	Tumour dissemination, paraplegia, bone disease	OPG transduced MSCs	[12]
MM.1S-GFP-Luc	$3 \times 10^6–1 \times 10^7$	i.v	28–56	300	Tumour dissemination	Melph, bort, anti-IGF, FAK/PyK2 inhibitor VS-4718, POL6926 CXCR7 antagonist	[8,13–16]
	0.5×10^6	i.t	14		Some tumour dissemination to other bones	POL6926 CXCR7 antagonist	[16]
U266	1×10^7	s.c	28–35	N/D	Tumour growth at site of injection, paraprotein	Galectin-3, bort, K-7174 proteosome inhibitor	[9,10]
Primary cells	$2 \times 10^5–2 \times 10^6$	i.c, i.o, i.v	42–157	300–340	Tumour dissemination, paraplegia, bone disease		[17]

Bort: bortezomib, iban: ibandronate, i.c: intracardiac, IGF: insulin-like growth factor, i.o: intraosseous, i.t: intratibial, i.v: intravenous, melph: melphalan, MSC: mesenchymal stem cell, N/D: not determined, OPG: osteoprotegerin, s.c: subcutaneous.