A Severe Combined Immunodeficient – hu In vivo Mouse Model of Human Primary Mantle Cell Lymphoma

Michael Wang,1 Liang Zhang,1 Xiaohong Han1,3 Jing Yang,1 Jianfei Qian,1 Sungyoul Hong,1 Pei Lin,2 Yuankai Shi,3 Jorge Romaguera,1 Larry W. Kwak,1 and Qing Yi1

Abstract

Purpose: To establish a severe combined immunodeficient (SCID)-hu in vivo mouse model of human primary mantle cell lymphoma (MCL) for the study of the biology and novel therapy of human MCL.

Experimental Design: Primary MCL cells were isolated from spleen, lymph node, bone marrow aspirates, or peripheral blood of six different patients and injected respectively into human bone chips, which had been s.c. implanted in SCID-hu. Circulating human β2-microglobulin in mouse serum was used to monitor the engraftment and growth of patient’s MCL cells. H&E staining and immunohistochemical staining with anti-human CD20 and cyclin D1 antibodies were used to confirm the tumor growth and migration.

Results: Increasing levels of circulating human β2-microglobulin in mouse serum indicated that the patient’s MCL cells were engrafted successfully into human bone chip of SCID-hu mice. The engraftment and growth of patient’s MCL cells were dependent on human bone marrow microenvironment. Immunohistochemical staining with anti-human CD20 and cyclin D1 antibodies confirmed that patient’s MCL cells were able to not only survive and propagate in the bone marrow microenvironment of the human fetal bone chips, but also similar to the human disease, migrate to lymph nodes, spleen, bone marrow, and gastrointestinal tract of host mice. Treatment of MCL-bearing SCID-hu mice with atipimod, a novel antitumor compound against the protection of bone marrow stromal cells, induced tumor regression.

Conclusion: This is the first human primary MCL animal model that should be useful for the biological and therapeutic research on MCL.

Mantle cell lymphoma (MCL), representing ~5% of all non–Hodgkin lymphoma, has the worst prognosis among all B-cell lymphomas, with median survival of 3 to 4 years (1–3). It is characterized by overexpression of cyclin D1 with a t(11;14) chromosomal translocation. Accurate diagnosis of MCL is based on morphology, immunophenotype (CD5+, CD19+, CD20+, CD10+, CD23±, IgM+, and IgD−), and detection of either the characteristic chromosomal translocation t(11;14) or overexpression of cyclin D1 (4, 5). Most MCL patients present with advanced stage disease, and up to 90% have involvement of the bone marrow, spleen, and/or gastrointestinal tract. MCL was shown to involve bone marrow in 92% of patients, although in some cases, the marrow infiltration was scarce and needed to be confirmed by repeated bone marrow biopsy and cytogenetic fluorescence in situ hybridization analysis (6).

MCL has a poor outcome and is a therapeutic challenge. Preclinical evaluation of investigational agents for MCL has been limited by lack of suitable animal models that mimic the natural history of human MCL and provide the microenvironment in which MCL cells thrive. The currently available in vivo model of MCL is s.c. xenograft of human MCL cell lines in severe combined immunodeficient (SCID) or nonobese diabetic–SCID mice (7, 8). This s.c. xenograft model does not mimic the microenvironment of human MCL cells in vivo nor is useful for primary MCL cells. Recently, murine MCL models were established by transgenic technique, and they may reveal important insights into the microenvironment and pathogenesis of the MCL (9, 10). However, MCL cells in the transgenic mouse models are murine, not human. Primary MCL cells from patients are very difficult to grow in culture medium in vitro and in the mouse model (11). Therefore, no human primary MCL in vivo model exists to date. This deficiency limits biological and therapeutic research on MCL. Because MCL usually involves the bone marrow, we developed an in vivo SCID model for human primary MCL cells. We adopted the SCID-hu mouse model developed for myeloma (12) and injected primary human MCL cells directly into the

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Marrow, and gastrointestinal tract. These cells metastasized to mouse lymph node, spleen, bone marrow, and gastrointestinal tract.

Materials and Methods

Patient samples. Specimens of spleen, lymph nodes, bone marrow aspirates, or peripheral blood were obtained from patients with MCL who gave informed consents. The sample collection protocol was approved by the Institutional Review Board at The University of Texas M. D. Anderson Cancer Center. Mononuclear cells were separated by Ficoll-Hypaque density centrifugation, and MCL cells were isolated using anti-CD19 antibody-coated magnetic microbeads (Miltenyi Biotec) and maintained in RPMI 1640 (Life Technologies) supplemented with 10% heat-inactivated fetal bovine serum, penicillin (10,000 units/mL; Sigma), streptomycin (10 mg/mL; Sigma), and 1-glutamine (29.2 mg/mL; Life Technologies).

Human fetal bone and drug. Fresh human fetal bones of 17 to 19 gestation wk were provided by Advanced Bioscience Resources. N-N-diethyl-8,8-dipropyl-2-azaspiro [4,5] decane-2-propanamine (atipristone), provided by Callisto Pharmaceuticals, was dissolved in PBS and injected i.p. to MCL-bearing mice at a dose of 50 mg/kg/d for 6 consecutive d.

SCID-hu mouse model. Six- to eight-week-old male CB-17 SCID mice (Harlan) were housed and monitored in our animal research facility. All experimental procedures and protocols had been approved by the Institutional Animal Care and Use Committee of The University of Texas M. D. Anderson Cancer Center. Procedures for SCID mouse implantation with human fetal bone grafts have been previously described (13–18). Approximately 4 to 6 wk after implantation, one injection of 0.5 to 5 × 10^6 purified patient MCL cells, depending on number of cells available after Ficoll-Hypaque density gradient centrifugation and immunomagnetic CD19+ sorting of mononuclear cells, was administered directly into human fetal bone implants within SCID-hu hosts or i.v. into tail vein after mice were anesthetized with ketamine (75 mg/kg) and xylazine (12.5 mg/kg; Lloyd). In some experiments, SCID mice, without implantation of human fetal bone chips, were used as controls.

ELISA. Levels of circulating human β2M in mouse serum were used to monitor tumor engraftment and growth in SCID-hu mice. Mouse blood was collected from tail vein weekly, and serum was used for measuring the levels of circulating human β2M using an ELISA kit (Alpha Diagnostic).

Histopathologic analysis. Excised tissues including human fetal bone grafts and mouse lymph nodes, spleen, liver, gastrointestinal tract, and femur were fixed in 10% formalin solution, processed by standard methods, embedded in paraffin, sectioned at 5 μm, and stained with H&E for histopathologic examination. For immunohistochemical evaluation, tissues were stained using monoclonal antibodies (mAb) specific for human CD20 (DAKO) and human cyclin D1 (GeneTex, Inc.). Slides were counterstained with Harris hematoxylin and examined by standard light microscopy. Samples were analyzed using an Olympus BX51TF microscope equipped with UPlan FL 40×/0.75 and 20×/0.50 objective lenses (Olympus). Pictures were taken using Olympus QColor 3 and analyzed using QCapture 2.60 software (QImaging).

Statistical analysis. Statistical significance of differences was determined using the Student’s t test. Differences were considered significant when P value was <0.05.

Results

Human fetal bone is critical for the engraftment of primary MCL cells in SCID-hu mice. Primary MCL cells were isolated from spleen, lymph node, bone marrow aspirates, or peripheral blood of six different patients with MCL and were used freshly or thawed after freezing in liquid nitrogen at -196°C. The purity of isolated MCL cells was confirmed to be >95% after purification by anti-CD19 antibody-coated magnetic microbeads (Miltenyi Biotec). The characteristics of these patients are presented in Table 1. The phenotype of the MCL cells from six patients was analyzed by flow cytometry and was

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Abbreviations: RTX, rituximab; REV, revlimid; VEL, velcade; MTX, methotrexate; CTX, cyclophosphamide; LDH, Lactate dehydrogenase; PB, peripheral blood; LN, lymph node; and BM, bone marrow.

*Hyper-CVAD indicates cyclophosphamide/vincristine/doxorubicin/dexamethasone.

1 Human β2M was detected at 3 wk after tumor inoculation.
CD5+CD19+CD20+CD23, which is characteristic of the immunophenotype of MCL. The tumor cells in each case were positive for cyclin D1.

We first evaluated the ability of patient MCL cells to engraft into the human bone marrow implanted in SCID-hu mice. The MCL cells were inoculated directly into human fetal bones in SCID-hu mice. To detect MCL engraftment and growth, we decided to monitor the levels of circulating human $\beta_2$M in the mice because human MCL cells, including both established cell lines and primary tumor cells from patients, produce and secrete $\beta_2$M (data not shown). After cell inoculation, mouse serum was collected weekly and was measured for human $\beta_2$M.

A total of 30 SCID-hu mice and 5 SCID mice were used for this study. Twenty of thirty SCID-hu mice were injected into human bone chips with primary MCL cells from six patients (2-5 SCID-hu mice per patient sample). Five of thirty SCID-hu mice and five SCID mice were injected i.v. via tail vein with $5.0 \times 10^6$ of patient MCL cells. Five of thirty SCID-hu mice were injected into human bone chips with equal volume of PBS and used as controls (Table 2). As shown in Fig. 1A to F, no human $\beta_2$M was detected in mice before or after human fetal bone implantation, indicating that antibodies used in the ELISA assay for measuring the levels of human $\beta_2$M do not crossreact with murine $\beta_2$M, and implanted human fetal bone marrow does not secrete detectable levels of human $\beta_2$M. However, human $\beta_2$M increased progressively after inoculation of patient MCL cells. SCID-hu mouse sera had detectable circulating human $\beta_2$M after 2 to 3 weeks of patient MCL cell inoculation. The increase in the levels of circulating human $\beta_2$M reflected the engraftment and subsequent growth of MCL tumors in the SCID-hu mice.

Primary MCL cell engraftment was observed in 15 of 20 SCID-hu mice injected into implanted human fetal bones and 1 of 5 SCID-hu mice by i.v. injection with primary MCL cells (Table 2). Both freshly isolated and cryopreserved cells were able to survive and establish MCL in SCID-hu mice. On one occasion, failed engraftments occurred with intrabone injections of $0.5 \times 10^6$ and $2 \times 10^6$, respectively, of thawed MCL cells isolated from

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*Direct injection into human fetal bone cavity.
† Intravenous injection via mouse tail vein. Data of each group are pooled from cells of patients 2 to 6.

![Fig. 1](http://www.aacrjournals.org/clinresearch/2008/14(7)/2156/fig1.png)

Fig. 1. Levels of circulating human $\beta_2$M in SCID-hu mice. Mouse serum was collected from tail veins weekly after inoculation of patient primary MCL cells and was detected for human $\beta_2$M by ELISA. A to F, six different MCL patient samples (pt.1-6). B to E, SCID-hu mice injected with freshly isolated primary MCL cells and (A and F) with thawed primary MCL cells. Each curve represents changes of circulating $\beta_2$M in one SCID-hu mouse. M, million.
For this purpose, the same number of primary MCL cells was necessary for the engraftment of tumor cells from patients. Isolated MCL cells had higher success rates than those with thawed cells. MCL cells, whether freshly isolated or cryopreserved, are able to increase in local tumor burdens of the SCID-hu bone chips (SCID-hu-MCL-bone), and (2) SCID-hu mice injected i.v. with MCL cells (SCID-MCL-iv). Mouse serum was collected from tail veins weekly after inoculation of patient primary MCL cells and was detected for human $\beta_2$M by ELISA. Data of each group are pooled data with tumor cells from all six patients.

Next, we examined whether the implanted human fetal bone was necessary for the engraftment of tumor cells from patients. For this purpose, the same number of primary MCL cells was injected i.v. via tail vein to SCID-hu mice or to SCID mice. SCID-hu mice receiving intrabone injection of PBS served as control. As shown in Table 2, only one of five SCID-hu mice had detectable human $\beta_2$M in mouse sera. Interestingly, in the SCID-hu mouse with a successful engraftment by i.v. injection of the tumor cells, a large tumor mass was observed around the implanted human bone 2 months after tumor inoculation, and the presence of MCL within and around the implanted human fetal bone was confirmed by histopathologic and immunohistochemical analyses (data not shown). Importantly, none of the five SCID mice injected i.v. with the same number of primary MCL cells developed tumors (Table 2). The levels of circulating human $\beta_2$M in the mice are shown in Fig. 2. The five SCID-hu mice receiving intrabone injection of the same number of primary MCL cells were used as positive controls. These data clearly indicate that human fetal bone provides a critical microenvironment for the survival and growth of primary MCL cells, and that primary MCL cells must be injected directly into implanted human bones in SCID-hu mice.

Patient MCL cells grow out of human bones and form expansile tumor masses surrounding the human bones. Figure 3 illustrates a typical engraftment and tumor burden in SCID-hu mice with primary MCL cells from patient 3. Flow cytometric analysis showed that purified MCL cells were $\text{CD}5^-\text{CD}19^+\text{CD}20^+\text{CD}23^-$ (Fig. 3A). Human $\beta_2$M in mouse serum was progressively increased after patient MCL cell inoculation (Fig. 3B). The rapid increase in serum levels of human $\beta_2$M coincided with the rapid increase in local tumor burdens of the SCID-hu bone chips (Fig. 3C, top). By week 12, these mice had to be sacrificed and human bone chips were removed. Higher levels of human $\beta_2$M were detected in mice injected with $5 \times 10^6$ of fresh MCL cells than mice injected with $2 \times 10^6$ or $0.5 \times 10^6$ fresh MCL cells.

Figure 3C shows the representative tumor masses from SCID-hu mice injected with different numbers of primary MCL cells. SCID-hu mice were sacrificed and tumors were removed. Mouse receiving injection of PBS showed the implanted fetal bones; however, for mice receiving injection of MCL cells, large tumor masses were recovered, indicating that MCL cells grew not only within the bone marrow but also outgrew from the bones. X-ray images of these tumors confirmed these results (Fig. 3C, middle). Interestingly, there was no bone destruction in the implanted human bones, which is different from myeloma–SCID-hu experiments.

To confirm that the increase in human $\beta_2$M was caused by the growth of patient MCL cells in the mice, we examined the pathology of decalcified sections of human bone implants. As shown in Fig. 3C (bottom), H&E staining showed that the human bone was fully packed with and surrounded by tumor cells. We examined the human bone sections with specific anti-human CD20 mAb by immunohistochemical staining. We observed cell-surface expression of human CD20 in clusters of cells in human bone marrow (Fig. 3D) and in its surrounding tumor mass (Fig. 3E). Thus, these results provide histologic evidence for the survival and growth of human primary MCL cells in the SCID-hu mice.

Human MCL cells home to mouse lymph node, spleen, bone marrow, and gastrointestinal tract. Lymph node, spleen, bone marrow, and gastrointestinal tract are the common sites of involvement by human MCL in patients. To confirm the specific homing of patient MCL cells into mouse hematopoietic organs, we harvested and evaluated a variety of mouse tissues from MCL-bearing SCID-hu mice. SCID-hu mice injected with PBS and SCID mice injected i.v. with patient MCL cells served as two control groups. Successful metastasis of patient MCL cells was identified by staining positive for human CD20. The results showed that inoculation of patient MCL cells into the implanted human bone chips of SCID-hu mice not only formed large tumor masses around the bones (Fig. 3C) but also metastasized to mouse lymph node, spleen, and bone marrow without the liver (Fig. 4A), as examined 2 months after tumor inoculation. Of interest is the result that human MCL cells were detected in the mouse gastrointestinal tract because it shows that similar to the human disease, patient MCL cells also micrometastasize to the murine gastrointestinal tract in addition to hematopoietic tissues (Fig. 4A). For the two control groups, no MCL cells were detected in tissues collected from PBS-treated SCID-hu or MCL-inoculated SCID mice (Fig. 4A).

To further confirm that human CD20 $^+$ B cells were MCL tumor cells, we examined their expression of cyclin D1. As shown in Fig. 4B, which shows a representative staining of consecutive sections of mouse spleen with anti-human CD20 or anti-human cyclin D1 mAbs, the cells stained positive for both human CD20 and cyclin D1, indicating that indeed, these cells were MCL tumor cells.

MCL–SCID-hu mouse model for testing the in vivo therapeutic efficiency of anti-MCL agent. Atiprimod is a novel cationic amphiphilic compound with strong antitumor activity against the protection of bone marrow stromal cells (19, 20). We recently found that atiprimod is an active agent in MCL, as it
inhibited the growth of MCL cell lines and freshly isolated MCL cells from patients, induced MCL cell apoptosis via activating mitochondria-mediated apoptosis pathways, and retarded the growth of s.c. inoculated MCL tumor cell lines in SCID mice (7). To evaluate the potential utility of this model to investigate the efficacy of therapeutic agents on primary MCL cells, we treated MCL-bearing SCID-hu mice (five per group) with i.p. injections of either PBS or atiprimod (50 mg/kg/day) for 6 consecutive days. Tumor growth was evaluated by measuring circulating human β2M by ELISA. As shown in Fig. 4C, treatment with atiprimod induced a dramatic tumor regression, evident by the decrease in the levels of circulating human β2M in serum of treated mice (P < 0.05, compared with control). These results indicate that this SCID-hu model not only allows for the study of MCL biology but also is useful for the preclinical evaluation of novel agents against MCL.

**Discussion**

Primary tumor cells such as myeloma and lymphoma usually do not survive and grow in SCID mice because they require the supporting human microenvironment. To establish a mouse model for primary myeloma cells, investigators developed SCID-hu mice, in which a fetal human bone chip was implanted s.c. into SCID mice (12). After a 4- to 6-week postprocedure recovery phase, the bone implants are found to be vascularized and histologically similar to normal human bone marrow and could provide bone marrow microenvironment for the growth of primary tumor cells (15). Injected myeloma cells grow within and around the bone chip and seldom migrate and infiltrate murine tissues (12). Through interactions with the human bone marrow microenvironment, myeloma cells induce typical myeloma manifestations, such as the appearance of M-protein in the serum, and changes in the density of implanted human bone. The SCID-hu mouse model has been used not only in studies of human hematopoiesis, immune function, and biological development (21–23) but also in studies of microenvironment and growth and metastasis of human primary myeloma cells in vivo (24).

MCL shares the same feature of common bone marrow involvement as myeloma. Previous studies indicated that MCL was identified in 83% to 92% of bone marrow aspirate specimens and in 91% of bone marrow biopsy specimens (6, 25, 26). Based on the characteristics of the high frequency of bone marrow involvement with MCL cells, we reasoned that by implanting a human fetal bone in SCID mice, primary MCL cells might survive and grow in the SCID mice. In this study, we successfully established a reproducible in vivo model closely resembling the clinical situation of patients with MCL. This approach is especially practical and useful because we can...
establish a mouse host by injecting as few as $0.5 \times 10^6$ of freshly isolated primary MCL cells from patients.

Unlike myeloma, MCL cells do not produce M-proteins. To monitor tumor growth, we examined various factors secreted by MCL cells such as IL-6, $\beta_2$-M, and lactate dehydrogenase (2, 3). Based on our preliminary studies monitoring and comparing serum levels of these factors and the sizes of tumor masses in MCL-bearing SCID-hu mice, we found a positive correlation between tumor burdens and the level of circulating human $\beta_2$-M. IL-6 and lactate dehydrogenase were less useful for this purpose. Therefore, we chose human $\beta_2$-M as the surrogate marker for tumor burden in MCL–SCID-hu mice. We recently showed that levels of circulating human $\beta_2$-M correlated well with the sizes of s.c. MCL tumors in the xenograft SCID mouse model (7). Therefore, circulating human $\beta_2$-M is indeed a good indicator for MCL tumor burdens in SCID-hu mice.

This study provides strong evidence for the crucial requirement of implanted human bone for the engraftment of primary MCL cells in the host. We injected primary MCL cells i.v. or directly into the bone chips of SCID-hu mice and found that intrabone, but not i.v. injection, led to the establishment of MCL in the majority of SCID-hu mice. Further support came from SCID mouse experiments in which i.v. injection of large numbers of primary MCL cells failed to establish MCL in the mice. Furthermore, in one of five SCID-hu mice that successfully engrafted MCL after i.v. injection of the tumor cells, a tumor mass formed within and around the implanted human fetal bone. These results indicate that the implanted bone chips are absolutely required, particularly during early stages of tumor engraftment, for injected MCL cells to survive and grow because at 2 months after tumor inoculation, primary MCL cells were also found in murine tissues such as bone marrow, lymph nodes, spleen, and gastrointestinal tract. This is a very interesting finding because in patients with MCL, tumor metastasis is often observed in these tissues or organs. About 5 years ago, gastrointestinal tract involvement was not common and in only $\approx 19\%$ of all cases (27). However, because Romaguera and coworkers (26) published results from their phase II study with 97 patients with MCL using Hyper CVAD regimen and found that 90% of patients were confirmed to have gastrointestinal tract involvement, gastrointestinal tract involvement by MCL at diagnosis has become very frequent (6). Therefore, we believe that our MCL–SCID-hu model will also be useful to elucidate the mechanisms underlying tumor metastasis in MCL.

The currently available mouse model for MCL is the xenograft SCID mouse model in which s.c. tumor burden is produced by injection of $5 \times 10^6$ of human MCL cell lines. Their growth characteristics are different from primary clinical
presentation. In addition, s.c. implantation of primary MCL cells was identified to be unsuccessful and impractical because up to $500 \times 10^6$ of primary tumor cells were required for inoculating each SCID mouse to establish MCL in some of the injected mice (11). In contrast, in our SCID-hu model, a minimum of $0.5 \times 10^6$ of primary MCL cells was able to survive and grow with a high success rate. Surprisingly, these primary MCL cells were able to migrate and homed to mouse lymph nodes, spleen, bone marrow, but not liver. Thus, this mouse model mimics the natural history of human MCL and the microenvironment that supports MCL survival. High engraftment rates with a short time for tumor establishment are required to make the in vivo model feasible for research purposes. We treated MCL-bearing SCID-hu mice i.p. with atiprimod for 6 consecutive days. Our data showed that atiprimod decreased serum $\beta_2$M to low levels, comparable with serum $\beta_2$M levels of mice treated with PBS. The results indicate that this SCID-hu model not only allows for the study of MCL biology but also is rapid and useful for the preclinical evaluation of novel agents against MCL.

Acknowledgments
We thank Alison Woo for providing editorial assistance.

References
Correction: A Severe Combined Immunodeficient–hu In Vivo Mouse Model of Human Primary Mantle Cell Lymphoma

In this article (Clin Cancer Res 2008;14:2154–60), which was published in the April 1, 2008, issue of Clinical Cancer Research (1), the authors mistakenly provided duplicate histology micrographs in Figs. 3C (H&E/0.5M) and 4A.
(spleen/MCL–SCID and liver/MCL–SCID-hu). After reviewing the original pathology data from the immunohistochemistry experiments, the authors have now identified and provided the correct images, which are included in the revised versions of Figs. 3 and 4. The conclusions set forth in the article remain unchanged. The authors regret this error.

Reference


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Michael Wang, Liang Zhang, Xiaohong Han, et al.

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