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Investigating the efficacy of bisphosphonates treatment against multiple myeloma induced bone disease using a computational model

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Abstract. Multiple myeloma (MM)-induced bone disease is mortal for most MM patients. Bisphosphonates are first-line treatment for MM-induced bone disease, since it can inhibit osteoclast activity and the resultant bone resorption by suppressing the differentiation of osteoclast precursors into mature osteoclasts, promoting osteoclast apoptosis and disrupting osteoclast function. However, it is still unclear whether bisphosphonates have an anti-tumour effect. In our previous work, a computational model was built to simulate the pathology of MM-induced bone disease. This paper extends this proposed computational model to investigate the efficacy of bisphosphonates treatment and then clear the controversy of this therapy. The extended model is validated through the good agreement between simulation results and experimental data. The simulation results suggest that bisphosphonates indeed have an anti-tumour effect.

Keywords: Multiple myeloma, MM-induced bone disease, bisphosphonates, anti-tumour, computational model

1. Introduction

Multiple myeloma (MM), a haematological malignancy developed in the bone marrow, is the most frequent cancer involving bone and the second most common cancer involving blood cells [1]. Bone disease, as a major complication of MM, is a fatal danger for MM patients. Up to 60% of MM patients suffer a fracture during the disease, and MM induced bone destruction rarely heals [2–5]. Bisphosphonates are first-line treatment for MM-induced bone disease [6]. Bisphosphonates are able to target high turnover skeletal sites and then bind to the mineralized bone matrix within these sites. After they are internalized by osteoclasts, bisphosphonates can inhibit osteoclast activity and the resultant bone resorption by suppressing the differentiation of osteoclast precursors into mature osteoclasts, promoting osteoclast apoptosis and disrupting osteoclast function. However, the further investigation is required

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to investigate the anti-tumour effects of bisphosphonates. Several preclinical and clinical data suggest that bisphosphonates may also have a direct anti-tumour effect or an indirect anti-tumour effect [7,8]. However, several studies provide contradictory results [9].

Computational modelling has demonstrated great potential in biological study [10–15]. In this paper, a previously developed computational model of MM-induced bone disease by Ji et al. [14] is extended to simulate bisphosphonates treatment against MM-induced bone disease. The simulation results can be used to investigate the efficacy of bisphosphonates and clear the controversy of the treatment.

2. Model development

The computational model proposed by Ji et al. [14] contains five variables (osteoblast precursors (OB_p), active osteoblasts (OB_a), active osteoclasts (OC_a), active MM cells (MM) concentrations and bone volume (BV)) and is made up of following equations:

$$\frac{dOB_p}{dt} = D_{OB_u} \cdot \pi_{act,OB_u}^{TGF\beta} \cdot OB_u - D_{OB_p} \cdot \pi_{rep,OB_p}^{TGF\beta} \cdot \pi_{rep,OB_p}^{VCAM1} \cdot OB_p \tag{1}$$

$$\frac{dOB_a}{dt} = D_{OB_p} \cdot \pi_{rep,OB_p}^{TGF\beta} \cdot \pi_{rep,OB_p}^{VCAM1} \cdot OB_p - A_{OB_a} \cdot \pi_{act,OB_a}^{VCAM1} \cdot OB_a \tag{2}$$

$$\frac{dOC_a}{dt} = D_{OC_p} \cdot \pi_{act,OC_p}^{RANKL} \cdot OC_p - \pi_{act,OC_a}^{TGF\beta} \cdot A_{OC_a} \cdot OC_a \tag{3}$$

$$\frac{dMM}{dt} = D_{MM} \cdot \pi_{act,MM}^{IL6} \cdot \pi_{act,MM}^{VCAM1} \cdot MM \cdot (1 - \frac{MM}{MM_{max}}) - A_{MM} \cdot \pi_{rep,MM}^{SLRPs} \cdot MM \tag{4}$$

$$\frac{dBV}{dt} = -K_{res} \cdot OC_a + K_{form} \cdot OB_a \tag{5}$$

which describe the temporal variations in OB_p, OB_a, OC_a, MM concentrations and BV respectively. The model uses 'Hill functions' to describe the cellular interaction via the single ligand to receptor binding through π functions [16]. The definitions of model parameters including OB_u, OC_p, MM_{max}, K_{res}, K_{form}, $TGF\beta$, $RANKL$, $VCAM1$, $IL6$ and $SLRPs$ are included in [14].

As shown in Eqs. (6) and (7), 'Hill functions' can both describe the stimulating and inhibiting functions of the ligand-receptor binding in the forms of $\pi_{act,\text{receptor}}^{ligand}$ and $\pi_{rep,\text{receptor}}^{ligand}$, respectively. $ligand$ in π functions represents the concentration of ligand in the ligand-receptor binding. q, p_1, p_2 and c are parameters related with π functions, and their definitions can be found in [14].

$$\pi_{act,\text{receptor}}^{ligand} = \frac{q \cdot (ligand)^c}{p_1 + (ligand)^c} \tag{6}$$

$$\pi_{rep,\text{receptor}}^{ligand} = \frac{q}{1 + (\frac{ligand}{p_2})^c} \tag{7}$$

In the simulation, the possible direct anti-tumour effects of bisphosphonates are not included in the model, since the further investigation is required to confirm this point. The model only considers the role of bisphosphonates inhibiting bone resorption by suppressing the differentiation of mature osteoc

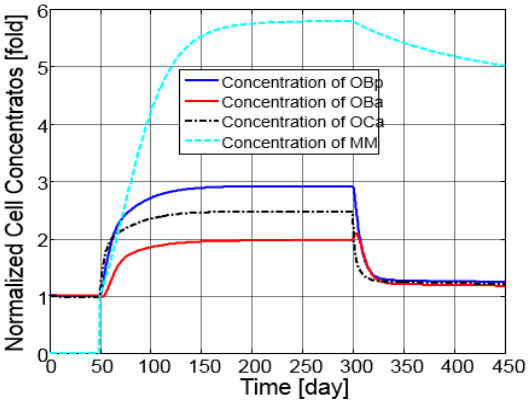

Fig. 1. The variation of normalized cell concentrations with respect to their initial value during different periods: the normal (healthy) period from day 1 to day 50, the invasion of MM cells from day 51 to day 300 and the intervention of the bisphosphonates therapy from day 301.

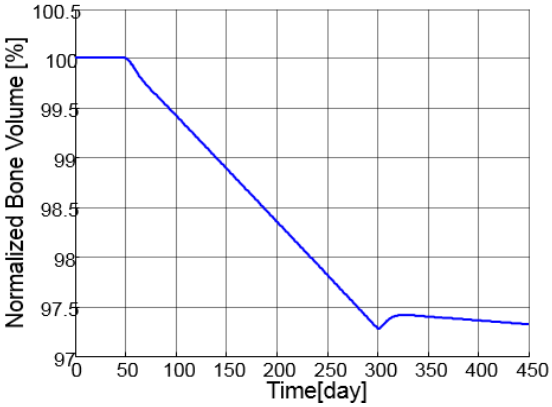

Fig. 2. The variation of normalized bone volume with respect to its initial value during different periods: the normal period from day 1 to day 50, the invasion of MM cells from day 51 to day 300 and the intervention of the bisphosphonates therapy from day 301.

lasts as well as promoting the apoptosis of osteoclasts. Thus a parameter 'F.Bi' which represents the degree that the bisphosphonates inhibit bone resorption, is introduced in Eq. (3) to represent the underlying mechanism of bisphosphonates treatment. The new equation is presented as follows:

$$\frac{dOC_a}{dt} = D_{OC_p} \cdot \pi_{act,OC_p}^{RANKL} \cdot OC_p \cdot \text{F.Bi} - \pi_{act,OC_a}^{TGF\beta} \cdot A_{OC_a} \cdot OC_a \cdot (1 + (1 - \text{F.Bi})) \quad (8)$$

for example, when 'F.Bi' is set as 0.7, it means that the differentiation rate of active osteoclasts decreases to 70% (0.7), while the apoptosis of osteoclasts increases by 30% (0.3 = 1 - 0.7). The previous computational model is extended to simulate the efficacy of bisphosphonates treatment through updating Eq. (3) by Eq. (8).

3. Simulation results

In this work, a genetic algorithm is implemented to estimate unknown model parameters. The Runge-Kutta (4th and 5th order) integration method, whose corresponding Matlab solver is ode45, is selected to solve the model equations. The parameters estimation and model equations solution are carried out in Matlab software (version: 7.6.0) [14]. The model solutions represent variations of in OB_p, OB_a, OC_a, MM concentrations and BV with time respectively.

Figures 1-3 demonstrate how a bisphosphonates therapy would influence cell concentrations and bone volume (F.Bi = 0.7). From day 1 to day 50, the bone microenvironment stays in the stable state where cell concentrations of OB_p, OB_a and OC_a, and bone volume nearly keep constant. MM cells appear from day 51, disturb the stable state of the bone microenvironment and consequently result in the variation of cell concentrations and bone volume. Figure 1 indicates that the bisphosphonates therapy reduces MM concentrations by 16% (for the period considered) and helps bone cell concentrations

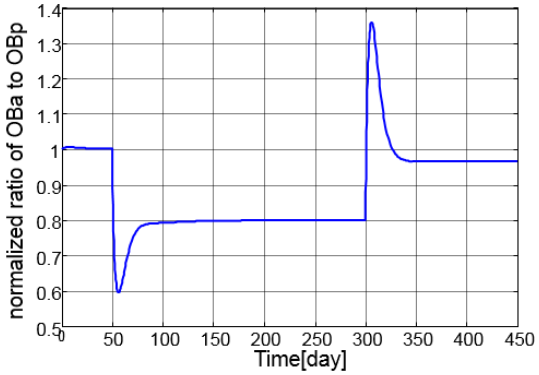

Fig. 3. The variation of normalized ratio of OBa:OCa with respect to its initial value during different periods: the normal period from day 1 to day 50, the invasion of MM cells from day 51 to day 300 and the intervention of the bisphosphonates therapy from day 301.

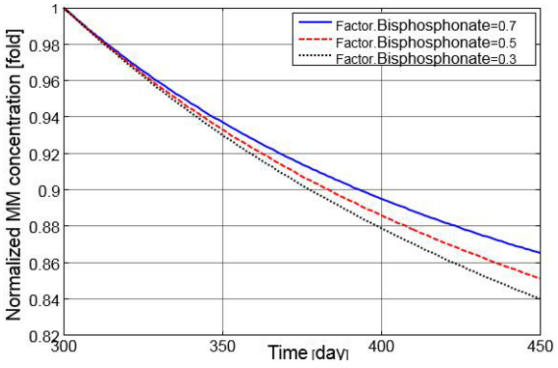

Fig. 4. The variation of normalized MM concentration with respect to the value at day 300 after use of the bisphosphonates therapy with different values of 'F.Bi'.

return to their normal values (i.e. values before the invasion of tumour cells). It is should be noted that the anti-tumour effects of bisphosphonates are not considered. Therefore the decreased tumour burden is due to the inhibited osteoclast activity by bisphosphonates, which agrees with the experimental conclusion that the decrease in osteoclast activity can inhibit the proliferation of MM cells [16,17]. As illustrated in Figure 3, the OBa:OCa ratio increases by 23% after the introduction of the bisphosphonates therapy, which thus results in a significant slowdown of the bone destruction (shown in Figure 2). Again, this is confirmed by published data that shows bisphosphonates are beneficial to the suppression of MM-induced bone destruction [18,19].

Figures 4-6 show the variations of MM concentration, bone volume and OB_a:OC_a ratio caused by bisphosphonates with different values of 'F.Bi' (0.7, 0.5 and 0.3) for the same treatment strategy. MM concentration decreases to 86.8%, 85.2% and 84% of its value at day 300 (for the period considered), when 'Factor.Bisphosphonate' is set as 0.7, 0.5 and 0.3 (shown in Figure 4). As illustrated in Figure 5, when 'F.Bi' is set as 0.7, the bone destruction continues although its rate is decreased dramatically, however when 'F.Bi' is set to 0.5 or 0.3, the bone destruction stops and bone volume begins to increase. Thus, the simulation results suggest that a smaller 'F.Bi' produces more significant inhibition of MM concentration and bone destruction. The decreased or ceased bone destruction shown in Figure 5 is due to the increasing OB_a:OC_a ratio caused by the bisphosphonate treatment demonstrated in Figure 6.

In Figures 1-6, the bisphosphonates treatment ends on day 450. The reason why day 450 is chosen as terminal time is that as demonstrated in Figures 1 and 3, the concentrations of OB_p, OB_a and OC_a, and OBa:OCa ratio nearly keep stable around day 450, and after day 450 the trends of curves regarding cell concentrations, bone volume (as shown in Figure 7) and OBa:OCa ratio keep the same pattern (the simulation of OBa:OCa ratio after day 450 is not given, because it can be calculated based on the data from the first figure in Figure 7).

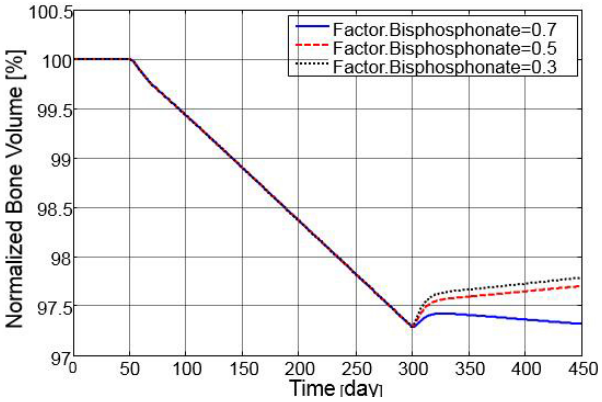

Fig. 5. The variation of normalized bone volume with respect to its initial value after use of the bisphosphonate therapy with different values of 'F.Bi'.

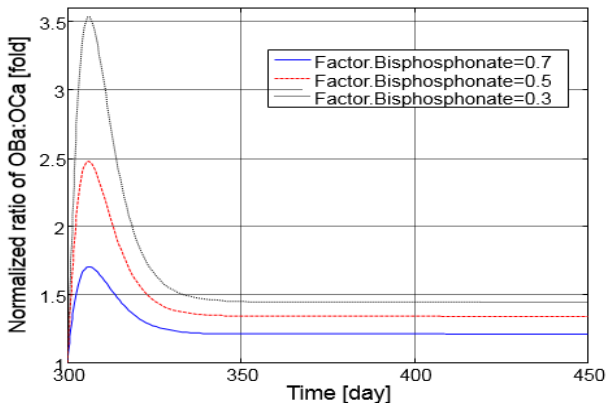

Fig. 6. The variation of normalized ratio of OBa:OCa with respect to the value at day 300 after use of the bisphosphonate therapy with different values of 'F.Bi'.

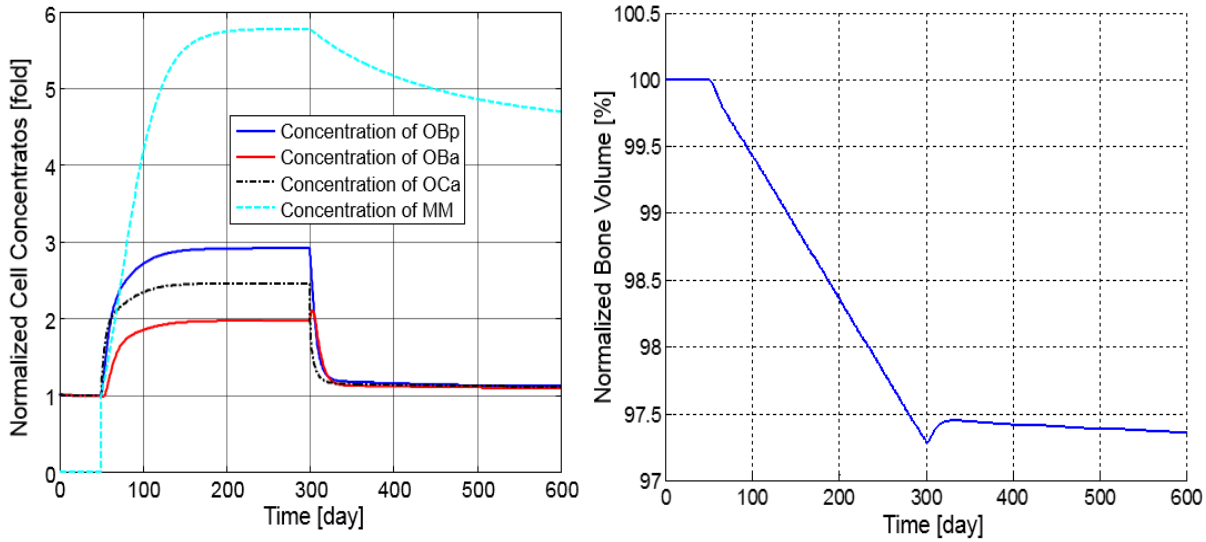

Fig. 7. The variation of normalized cell concentrations and bone volume with respect to their initial value during different periods: the normal (healthy) period from day 1 to day 50, the invasion of MM cells from day 51 to day 300 and the intervention of the bisphosphonates therapy from day 301 to day 600 (F.Bi=0.7).

4. Conclusion

In this paper, a computational model of MM-induced bone disease developed in our previous work [14] is extended to simulate the underlying mechanism of the bisphosphonates treatment. The extended computational model is able to simulate how the invasion of MM cells disturbs the stable state of the bone microenvironment and causes the fluctuation of cell concentrations and bone volume, and how the bisphosphonates treatment helps cell concentrations and bone volume return to their normal (healthy) values. The model results compare with published experimental data well and also demon-

strate that the bisphosphonates treatment is effective in the management of MM-induced bone disease, since it can not only suppress osteoclast activity and the resultant bone resorption, but also has anti-tumour effects which then helps to get rid of the controversy whether the bisphosphonates treatment has anti-tumour effects.

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