

doi: 10.13241/j.cnki.pmb.2015.17.014

阿仑膦酸钠联合化疗对多发性骨髓瘤患者骨代谢的影响

饶进 殷莉[△] 林志美 熊萍 苟晓琴

(成都大学附属医院血液科 四川 成都 610081)

摘要 目的:研究阿仑膦酸钠联合化疗对多发性骨髓瘤患者骨代谢的影响。**方法:**选取 2011 年 4 月到 2014 年 4 月我院收治的多发性骨髓瘤患者 130 例,按照随机数字表法将患者分为研究组和对照组,每组 65 例,对照组给予化疗,研究组在对照组的基础上给予阿仑膦酸钠,比较两组骨特异性碱性磷酸酶(BAP)、骨钙素(OC)、I 型前胶原氨基肽(PINP)、血钙(Ca)、血磷(P)、β 胶原特殊序列(β-CTx)以及碱性磷酸酶(ALP)。**结果:**治疗后研究组 OC、PINP 和 BAP 均显著高于治疗前和对照组,比较差异均有统计学意义($P < 0.05$);治疗后研究组 β-CTx 显著低于治疗前和对照组,比较差异均有统计学意义($P < 0.05$)。**结论:**阿仑膦酸钠联合化疗治疗多发性骨髓瘤患者能显著改善其的骨代谢,值得临床推广。

关键词:阿仑膦酸钠;化疗;多发性骨髓瘤;疗效

中图分类号:R733.3 **文献标识码:**A **文章编号:**1673-6273(2015)17-3253-03

The Effect of Alendronate in Combination with Chemotherapy on Bone Metabolism in Patients with Multiple Myeloma

RAO Jin, YIN Li[△], LIN Zhi-mei, XIONG Ping, GOU Xiao-qin

(Department of Hematology, The Affiliated Hospital of Chengdu University, Chengdu, Sichuan, 610081, China)

ABSTRACT Objective: To study the effect of alendronate in combination with chemotherapy on bone metabolism in patients with multiple myeloma. **Methods:** 130 cases with multiple myeloma who treated in our hospital from April 2011 to April 2014 were selected, they were divided into the study group and the control group according to a random number table, 65 cases in each group, the patients of the control group were treated with chemotherapy, the patients of the study group were given alendronate on the basis of the control group, bone-specific alkaline phosphatase (BAP), osteocalcin (OC), I procollagen amino-peptide (PINP), calcium, phosphorus, β collagen special sequences (β-CTx) and alkaline phosphatase of two groups were compared. **Results:** After treatment, the OC, PINP and BAP of the study group were significantly higher than before treatment and the control group, the difference was statistically significant ($P < 0.05$); The β-CTx of the study group were significantly lower than before treatment and the control group, the difference was statistically significant ($P < 0.05$). **Conclusion:** Alendronate combination with chemotherapy in treatment of multiple myeloma can significantly improve bone metabolism. It is worthy of clinical promotion.

Key words: Alendronate; Chemotherapy; Multiple myeloma; Efficacy Chinese Library

Chinese Library Classification(CLC): R733.3 **Document code:** A

Article ID: 1673-6273(2015)17-3253-03

前言

多发性骨髓瘤是恶性的浆细胞瘤,来源于骨髓内的浆细胞,是属于 B 淋巴细胞瘤^[1,2]。化疗治疗多发性骨髓瘤具有较好的临床疗效,但是由多发性骨髓瘤引起的骨病却效果较差,溶骨性的骨质被破坏是多发性骨髓瘤的常见临床表现^[3,4]。阿仑膦酸钠具有抑制破骨细胞的作用,能治疗各种类型的骨质疏松症。但是,应用阿仑膦酸钠治疗多发性骨髓瘤引起的骨病缺乏临床研究,其临床效果也尚不确定^[5,6]。本研究旨在分析阿仑膦酸钠联合化疗对多发性骨髓瘤患者骨代谢的影响,进而为临床治疗提供依据,现将结果报道如下。

作者简介:饶进(1972-),女,本科,副主任医师,从事血液肿瘤方面的研究, E-mail: raojin_6364@163.com

[△]通讯作者:殷莉(1983-),女,硕士,住院医师,从事白血病多药耐药方面的研究, E-mail: yinli_3624@163.com

(收稿日期:2015-01-19 接受日期:2015-02-13)

1 材料与方法

1.1 一般材料

选取 2011 年 4 月到 2014 年 4 月我院收治的多发性骨髓瘤患者 130 例,所有患者均符合多发性骨髓瘤的诊断标准^[4],且均未接受其他治疗,并排除合并严重内科疾病者、其他恶性肿瘤患者。按照随机数字表法将患者分为研究组和对照组,每组各 65 例。研究组男性 35 例,女性 30 例;年龄 49-80 岁,平均年龄(68.3 ± 2.3)岁。对照组男 34 例,女性 31 例;年龄 50-80 岁,平均年龄(67.9 ± 1.9)岁。两组年龄和性别比较均无显著差异($P > 0.05$),具有可比性,研究经伦理委员会批准,所有患者均知情同意并签订知情同意书。

1.2 治疗方法

对照组:给予常规化疗,主要的化疗方案有 VAD(长春瑞滨+表柔比星+地塞米松);COMP(环磷酰胺+长春瑞滨+马法兰+泼尼松)。研究组:在对照组的基础上给予阿仑膦酸钠

(生产厂家:默沙东制药有限公司生产,批准文号:国药准字J20080073)治疗,70 mg/次,每周1次,于清晨空腹服用,服用以后需要饮用清水500 ml,并且将上身保持直立大约半个小时。两组治疗时间均为6个月。

1.3 观察指标

比较两组治疗前和治疗后骨特异性碱性磷酸酶(BAP)、骨钙素(OC)、I型前胶原氨基肽(PINP)、血钙(Ca)、血磷(P)、β胶原特殊序列(β-CTX)和碱性磷酸酶(ALP)。抽取所有入选者治疗前后的清晨空腹静脉血液5ml,其中血钙、碱性磷酸酶以及血磷应用全自动生化分析仪器检测(罗氏7600),其他指标均应用酶联免疫吸附试验(ELISA)进行检测,所应用的试剂均来自Beckman Access公司,由专业人员进行操作,并且根据试剂

盒上的操作说明进行操作。

1.4 统计学方法

全部数据均在SPSS17.0软件上统计,其中计量资料用($\bar{x} \pm s$)表示,应用t检验,计数资料应用 χ^2 检验,检验标准以 $P < 0.05$ 表示有统计学意义。

2 结果

2.1 两组一般情况比较

由表1可知,两组的亚型、化疗方案、临床分期、合并骨病以及免疫分型均无显著差异,两组比较差异无统计学意义($P > 0.05$),见表1。

表1 两组一般资料比较

Table 1 Comparison of the general information of two groups

组别 Groups	例数 Cases	免疫分型 Immunophenotyping		亚型 Subtype		临床分期 Clinical stage		化疗方案 Chemotherapy		合并骨病 Merge bone disease
		IgG	IgG	A	B	II	III	VAD	COMP	
对照组 Control group	65	47	13	34	26	30	30	42	18	58
研究组 Study group	65	46	12	35	25	29	31	41	19	57
χ^2		3.093		2.098		3.893		4.078		5.089
P		0.098		0.104		0.087		0.079		0.069

2.2 两组骨代谢指标比较

由表2可知,治疗后研究组OC、PINP和BAP均显著高于治疗前和对照组,比较差异均有统计学意义($P < 0.05$);治疗后

研究组β-CTX显著低于治疗前和对照组,比较差异均有统计学意义($P < 0.05$),见表2。

表2 两组骨代谢指标比较($\bar{x} \pm s$)

Table 2 Comparison of index of bone metabolism between two groups ($\bar{x} \pm s$)

指标 Indexes	对照组 Control group		研究组 Study group	
	治疗前 Before treatment	治疗后 After treatment	治疗前 Before treatment	治疗后 After treatment
BAP(ug/L)	5.63± 0.25	5.71± 0.18	5.54± 0.78	9.82± 0.52 ^{ab}
PINP(ug/L)	87.49± 1.92	88.67± 3.07	86.58± 2.07	106.8± 2.73 ^{ab}
OC(ug/L)	11.59± 0.58	11.83± 2.49	11.53± 1.78	14.02± 1.64 ^{ab}
β-CTX(ug/L)	1.51± 0.21	1.43± 0.32	1.53± 0.72	1.19± 0.78 ^{ab}
Ca(mmol/L)	2.54± 0.02	2.55± 0.04	2.53± 0.01	2.56± 0.05
P(mmol/L)	1.26± 0.03	1.27± 0.14	1.26± 0.04	1.29± 0.06
ALP(U/L)	87.13± 2.07	88.28± 8.02	87.02± 7.03	88.32± 0.15

注:与治疗前比较,^a $P < 0.05$;与对照组比较,^b $P < 0.05$ 。

Note: Compared with before treatment,^a $P < 0.05$; compared with the control group,^b $P < 0.05$.

3 讨论

多发性骨髓瘤患者多伴随着骨病,据不完全统计,初诊时多发性骨髓瘤患者的骨病发生率高达73.2%,提示骨病是多发性骨髓瘤患者临床常见疾病^[7-9]。临床上治疗多发性骨髓瘤多重视原发病的治疗,对于其他伴发疾病则容易忽视。所以临床上治疗多发性骨髓瘤伴发的骨病经验较少^[10-12]。多发性骨髓瘤患者的骨病是由破骨细胞和骨细胞造成的,骨的重吸收能力增

加,但是新骨形成则受到抑制。许多研究都已证实,多发性骨髓瘤患者细胞浸润的局部出现的破骨细胞数量显著增加,多发性骨髓瘤细胞和骨髓中的微环境作用,在激活破骨细胞的形成和抑制成骨细胞的活性中起到重要作用^[13]。临床上化疗对多发性骨髓瘤具有一定的临床疗效,但是对于其伴随骨病效果甚微,对多发性骨髓瘤患者的骨代谢无显著影响^[14,15]。阿仑膦酸钠是一种常用于临床的治疗骨病的药物,具有抵抗骨吸收的作用,现阶段常用来治疗骨质疏松症,该药物服用以后被人体吸收,

然后会在骨的吸收表面沉积,并且可以被破骨细胞所摄取,能于破骨细胞周围积聚,进而起到抑制破骨细胞的活性的作用,最终减少骨的吸收^[16-18]。对于多发性骨髓瘤患者的主要作用机制是破骨细胞造成的骨的重吸收能力增加有较好的效果^[19]。

本研究对患者进行6个月的治疗,通过治疗前后比较以及两组间的比较可以发现,两组的亚型、化疗方案、临床分期、合并骨病以及免疫分型均无显著差异,提示一般资料无显著差异,对研究结果的影响作用较小,给实验带来的误差也会较小。研究发现,治疗后研究组OC、PINP和BAP均显著高于治疗前,且显著高于对照组;治疗后研究组 β -CTX显著低于治疗前,与治疗前比较差异具有统计学意义($P < 0.05$),且显著低于对照组,与对照组比较差异具有统计学意义($P < 0.05$),与其他研究结果具有一致性^[6,15,20],提示阿仑膦酸钠联合化疗相比单独应用化疗对多发性骨髓瘤患者的骨代谢效果更好,能显著改善患者的骨代谢,减少骨破坏。

综上所述,骨代谢异常是多发性骨髓瘤患者常见的伴发疾病,单独化疗对骨代谢影响较大,阿仑膦酸钠联合化疗治疗多发性骨髓瘤能显著改善患者的骨代谢,具有较好的临床疗效。

参考文献(References)

- [1] Wang K, Xu Z, Wang N, et al. MicroRNA and gene networks in human diffuse large B-cell lymphoma [J]. *Oncol Lett*, 2014, 8(5): 2225-2232
- [2] Kang AR, Oh YR, Kim HY, et al. Up-regulation of inhibitors of DNA binding/differentiation gene during alendronate-induced osteoblast differentiation[J]. *Arch Gynecol Obstet*, 2012, 285(5): 1331-1338
- [3] Shane E, Cohen A, Stein EM, et al. Zoledronic Acid Versus Alendronate for the Prevention of Bone Loss after Heart or Liver Transplantation [J]. *J Clin Endocrinol Metab*, 2012, 97(12): 4481-4490
- [4] Smita Nayak, Mark S. Roberts, Susan L. Greenspan. Impact of Generic Alendronate Cost on the Cost-Effectiveness of Osteoporosis Screening and Treatment[J]. *PLoS One*, 2012, 07(03): e32879
- [5] Brenda M, Birmann ML, Neuhauser BR, et al. Prediagnosis biomarkers of insulin-like growth factor-1, insulin, and interleukin-6 dysregulation and multiple myeloma risk in the Multiple Myeloma Cohort Consortium[J]. *Blood*, 2012, 13(25): 4929-4930
- [6] Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women[J]. *Osteoporos Int*, 2013, 23(1): 317-326
- [7] Aksungar FB, Ayer M, Serteser M, et al. A triclonal gammopathy in a relapsing multiple myeloma patient, detected by immunosubtraction method[J]. *Annals of clinical biochemistry*, 2014, 51(5): 606-610
- [8] Wen J, Li H, Tao W, et al. High throughput quantitative reverse transcription PCR assays revealing over-expression of cancer testis antigen genes in multiple myeloma stem cell-like side population cells [J]. *British journal of haematology*, 2014, 166(5): 711-719
- [9] Bringhen S, Gay F, Donato F, et al. Current Phase II investigational proteasome inhibitors for the treatment of multiple myeloma [J]. *Expert opinion on investigational drugs*, 2014, 23(9): 1193-209
- [10] Wang F, Xing T, Li J, et al. Coexisting glomerular IgA deposition and IgG-kappa multiple myeloma [J]. *Renal failure*, 2014, 36(8): 1345-1347
- [11] Matsui W, Borrello I, Mitsiades C. Autologous stem cell transplantation and multiple myeloma cancer stem cells [J]. *Biol Blood Marrow Transplant*, 2012, 18(1): S27-32
- [12] Yang J, He J, Wang J, et al. Constitutive activation of p38 MAPK in tumor cells contributes to osteolytic bone lesions in multiple myeloma[J]. *Leukemia*, 2012, 26(9): 2114-2123
- [13] Yun H, Curtis JR, Saag K, et al. Generic Alendronate Use among Medicare Beneficiaries: Are Part D Data Complete? [J]. *Pharmacoepidemiol Drug Saf*, 2013, 22(01): 55-63
- [14] Mok JO, Jung CH, Kim CH, et al. Endoscopic comparison of alendronate alone and the enteric-coated alendronate with calcitriol combination in postmenopausal Korean females [J]. *Korean J Intern Med*, 2013, 28(6): 694-700
- [15] Gómez Acotto C, Antonelli C, Flynn D, et al. Upper Gastrointestinal Tract Transit Times of Tablet and Drinkable Solution Formulations of Alendronate: A Bioequivalence and a Quantitative, Randomized Study using Video Deglutition[J]. *Calcif Tissue Int*, 2012, 91(05): 325-334
- [16] 刘雄. 阿仑膦酸钠治疗原发性骨质疏松症的4年临床研究[J]. *现代生物医学进展*, 2009, 9(24): 4722-4724
- [17] Liu Xiong. The efficacy of 4 years alendronate therapy in patients with primary osteoporosis[J]. *Progress in Modern Biomedicine*, 2009, 9(24): 4722-4724
- [18] Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma [J]. *Leukemia*, 2014, 28(02): 258-268
- [19] Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma [J]. *Blood*, 2012, 119(13): 3003-3015
- [20] Josefsson Ben-Yehoshua L, Beider K, Shimoni A, et al. Characterization of Cyclin E Expression in Multiple Myeloma and Its Functional Role in Seliciclib-Induced Apoptotic Cell Death [J]. *PLoS One*, 2012, 07(04): e33856
- [21] Papanikolaou X, Szymonifka J, Rosenthal A, et al. Metronomic therapy is an effective salvage treatment for heavily pre-treated relapsed/refractory multiple myeloma[J]. *Haematologica*, 2013, 98(7): 1147-1153