DOI: 10.13241/j.cnki.pmb.2014.02.052

乳腺癌双膦酸盐辅助治疗临床研究进展

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摘要:乳腺癌是女性发病率和死亡率最高的恶性肿瘤,复发和远处转移仍是导致患者死亡的首位原因,而双膦酸盐作为一种骨质吸收抑制剂,能够抑制破骨细胞介导的骨质吸收,在多种实体肿瘤骨转移及多发性骨髓瘤等恶性疾病所致的骨相关事件治疗中起重要作用。近年来大量体外、体内实验表明双膦酸盐还具有抑制肿瘤细胞生长、粘附、播散和侵润,降低肿瘤细胞膜稳定性、促进肿瘤细胞凋亡等直接抗肿瘤作用以及抑制肿瘤血管生成、激活免疫细胞对肿瘤细胞的杀伤等间接抗肿瘤作用,基于这些基础研究结果已经开展了一系列针对双膦酸盐辅助治疗乳腺癌的临床试验研究,本文就近年相关临床试验研究进展做简要综述。

关键词:乳腺癌;双膦酸盐;临床研究

中图分类号:R737.9 **文献标识码**:A **文章编号**:1673-6273(2014)02-393-04

Clinical Advances of Adjuvant Bisphosphonates in Breast Cancer

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ABSTRACT: Breast cancer is by far the most common malignancy in women and it is ranked as the leading cause of cancer death. However, relapse and metastasis are still the primary reason for mortality, and bisphosphonates have been used as an inhibitor of bone resorption by inhibiting resorption mediated by osteoclasts to treat skeletal-related events in patients with bone metastases and multiple myeloma early. Recently, based on a lot of evid ence of anticancer activity of bisphosphonates in vivo and in vitro, these results suggest that bisphosphonates can Inhibit tumor growth, adhesion, spreading and infiltration, as well as reduce membrane stability of tumor cell and promote apoptosis of tumor cells. Moreover, bisphosphonates have other indirect antitumor effects including inhibition of tumor angiogenesis and activation of the immune cell cytotoxicity on tumor cells. A great many clinical trials assessing antitumor effects and anticancer applications of adjuvant bisphosphonates in breast cancer have been conducted. This article reviews clinical advances of adjuvant bisphosphonates in breast cancer according to a variety of results of clinical trials on these issues in recent years.

Key words: Breast neoplasms; Bisphosphonates; Clinical Trial

Chinese Library Classification: R737.9 Document code: A

Article ID :1673-6273(2014)02-393-04

前言

乳腺癌是女性发病率和死亡率最高的恶性肿瘤,肿瘤复发和远处转移是导致患者死亡的首位原因[1]。其中,骨转移为最常见的复发转移部位,转移性乳腺癌患者中有 80%的患者发生骨转移。骨转移会导致严重的并发症如疼痛和骨相关事件。双膦酸盐作为一种骨质吸收抑制剂,能够抑制破骨细胞介导的骨质吸收,临床用于肿瘤骨转移及多发性骨髓瘤等恶性疾病所致骨相关事件的治疗[2]。双膦酸盐属于焦膦酸盐化合物的一种类似物, 其基本分子骨架结构由两个磷原子和一个碳原子(P-C-P)组成,同时包括 R1 和 R2 两条侧链。其中,R2 侧链可为含氮基团或非含氮基团。含氮双膦酸盐如帕米膦酸盐、伊班膦酸盐和唑来膦酸,非含氮双膦酸盐包括氯膦酸盐、依替膦酸盐等,含氮双膦酸盐的抗骨质吸收作用强于非含氮双膦酸盐。此外,两类双膦酸盐抗骨质吸收的作用机制亦不相同,非含氮双膦酸盐主要通过抑制 ATP 依赖的酶而抑制破骨细胞活性, 含氮双膦酸盐一方面可作为钙螯合剂在细胞外稳定骨基质钙磷代谢,另一方面可以通过甲羟戊酸信号途径在破骨细胞内发挥作用,包括调控脂质代谢的转录后调控和小分子 GTP 酶在细胞膜的锚定,这也是双膦酸盐发挥潜在抗肿瘤效果的作用基础[3,4]。近年来大量体外、体内实验表明双膦酸盐还具有抑制肿瘤细胞的生长、粘附、播散和侵润,降低肿瘤细胞膜稳定性、促进肿瘤细胞凋亡等直接抗肿瘤作用以及抑制肿瘤新生血管形成、激活免疫细胞对肿瘤细胞的杀伤作用并协同化疗药物等间接的抗肿瘤作用[5-8]。为了验证双膦酸盐在乳腺癌辅助治疗中的实际效果,目前已经开展了大量的临床试验,其整体研究形式呈逐年增加趋势(见图 1),现就最新研究进展做如下综述。

1 双膦酸盐的抗肿瘤机制

既往大量临床前期研究表明双膦酸盐具有直接的抗肿瘤作用。体内实验研究结果显示双膦酸盐可以通过 Caspase 途径诱导肿瘤细胞的凋亡,多种双膦酸盐中以唑来膦酸的作用最为显著且作用效果与药物剂量相关[9]。双膦酸盐也可以抑制肿瘤细胞的粘附、侵润进而抑制其转移。Boissier 等学者发现经双膦

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(收稿日期:2013-05-02 接受日期:2013-05-28)

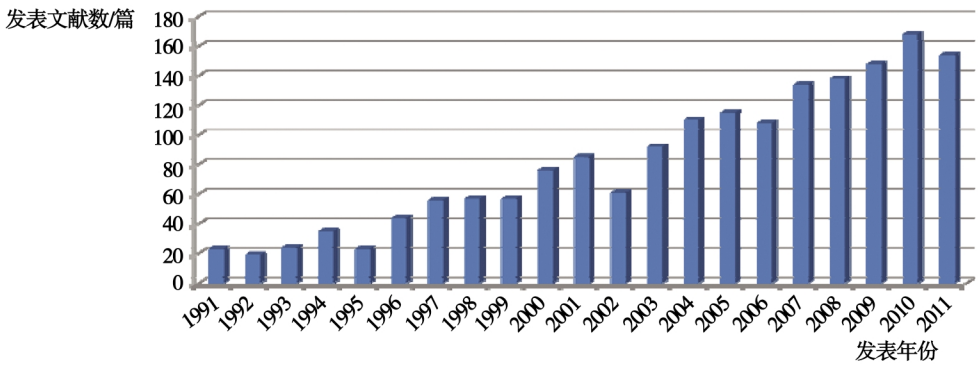

图 1 1991~2011 年乳腺癌双膦酸盐辅助治疗研究论文发表情况(PubMed,关键词:乳腺癌、双膦酸盐)

Fig.1 Publications of adjuvant bisphosphonates in breast cancer between 1991 and 2011(PubMed, keywords: breast neoplasms; bisphosphonates)

酸盐处理后,人乳腺癌 MCF-7 和 MDA-MB-231 细胞对矿化和非矿化骨基质的粘附能力均下降。在另一项实验研究中他们还发现双膦酸盐也可以抑制肿瘤细胞对人造基底膜的侵润能力。同时,双膦酸盐对肿瘤细胞粘附、侵润能力的抑制呈现一定的剂量依赖性[10]。此外也有研究表明双膦酸盐可以通过抑制内皮细胞增殖,降低血小板衍生生长因子、内皮细胞生长因子的水平而抑制肿瘤新生血管形成。同时双膦酸盐还可以活化免疫细胞,促进免疫细胞成熟并上调 γ 干扰素水平,从而增强免疫细胞的肿瘤杀伤功能[11,12]。

2 双膦酸盐抗肿瘤作用的临床研究

随着各种辅助检查技术的提高以及乳腺癌普查工作的广泛开展,早期乳腺癌的诊出率和生存率都明显提高。但由于乳腺癌在疾病早期即可发生血行转移,仍有部分病例发生肿瘤复发、转移。鉴于既往临床前基础研究发现的双膦酸盐所具有直接、间接抗肿瘤作用,已有多项临床试验评估了几种临床常用双膦酸盐类药物在早期乳腺癌辅助治疗中的作用[13]。

2.1 氯膦酸盐

最先探讨氯膦酸盐对乳腺癌复发、侵润影响的是 Elomaa 及其同事[14]开展的口服氯膦酸盐(1600 mg/ 天)或安慰剂的病例对照研究(n=34),随访 12 个月后发现口服氯膦酸盐患者的生存率高于安慰剂组。其后,Diel 等[15]设计开展了首个研究口服氯膦酸盐对早期乳腺癌复发、生存影响的随机对照试验,该研究共入组乳腺癌术后骨髓弥散肿瘤细胞检测阳性的患者 302 人,随机分组并随访 36 个月后发现,行辅助治疗同时口服氯膦酸盐(2 年,1600 mg/ 天)组患者的骨转移率(8% vs 17%, P=0.003)及内脏转移率(13% vs 29%,P<0.001)均低于仅接受辅助治疗的患者,同时患者的总生存率提高(P<0.001),随访 103± 12 个月时仍保持治疗优势,尽管两组患者骨转移和内脏转移率差异无统计学意义,但总生存率的提高仍有意义,提示患者长期服用氯膦酸盐对总生存率的提高仍是具有临床意义的[16]。但芬兰学者 Saarto 的研究结果却得出相反结论,该研究探讨口服氯膦酸盐(3 年,1600 mg/ 天)是否可以降低淋巴结阳性乳腺癌患者骨转移的发生率,随访 5 年发现,与安慰剂组相比,口服氯膦酸盐并不能降低患者骨转移发生率(21% vs 17%, P=0.27,n=299), 总生存率及无病生存率反而低于对照组(OS 70% vs 83%, P=0.009; DFS 56% vs 71%, P =0.007)[17]。其后随访 10 年人未得到阳性结果,患者 DFS 仍低于安慰剂组(45% vs. 58%, P=0.01),但此时两组患者 OS 差异不存在统计学意义,据此研究者认为口服氯膦酸盐会对淋巴结阳性患者的 DFS 有负面影响[18]。随后,Powles 等[19]进行了一项规模更大的临床随机对照试验,该试验共纳入 1069 名Ⅰ-Ⅲ期可手术乳腺癌患者并随机分为口服氯膦酸盐组(2 年,1600 mg/ 天)或安慰剂组。随访 5.6 年发现, 氯膦酸盐组骨转移风险低于安慰剂组(HR=0.692, P=0.043,这一差异在Ⅱ-Ⅲ期肿瘤患者中更为明显(HR=0.592, P=0.009),患者 OS 也高于安慰剂组(P=0.048),显示存活收益。面对上述迥异的试验结果,一项纳入 1966~2006 年期间 13 项临床试验的系统综述分析了口服氯膦酸盐 (2~3 年,1600mg/ 天)对早期乳腺癌患者总存活的影响[20]。结论认为乳腺癌患者 5 年总生存率、无骨转移生存率、及无骨外转移生存率等与其是否口服氯膦酸盐并无明显关系。而最新公布的研究口服氯膦酸盐是否能够为乳腺癌患者带来存货收益的规模最大的 NSABP-B-34 试验[21],这是一项多中心、随机、双盲、安慰剂对照的三期临床试验, 共纳入 3323 例Ⅰ-Ⅲ期乳腺癌患者,随访 90.7 个月后,两组患者的 DFS、OS、无骨转移生存率及无复发生存率差异均无统计学意义,仅无骨外转移生存率稍有提高(P=0.047),进一步对绝经后患者的亚组分析结果显示,年龄较大的绝境后患者服用氯膦酸盐后, 尽管总生存率无明显改变,但无复发生存率、无骨转移生存率及无骨外转移生存率均有所提高。

2.2 帕米膦酸盐及伊班膦酸盐

目前有关帕米膦酸盐辅助治疗乳腺癌的临床证据还十分有限,仅为几项小规模试验。Conte 等[22]发现(n=372)发生骨转移的乳腺癌患者行化疗同时加用帕米膦酸盐可以延缓骨转移灶的疾病进展时间(249 vs 168 天; P=0.02)。Kokufu 等学者也发现,存在 4 枚或 4 枚以上淋巴结转移的患者(n=90)接受帕米膦酸盐(45 mg,4 次 /2 周)治疗并随访 5 年后,骨转移的发生率显著低于对照组(12.1% vs 40.4%,P=0.005),其无骨转移生存率也高于对照组 (85.9% vs 64.0%, P=0.023)[23]。但 van Holten-Verzantvoort 等实施的早期临床试验(n=124)却并未得出类似结论,与对照组相比,尽管口服帕米膦酸盐(300 mg/ 天)并未降低或延缓骨转移的发生,但局部晚期或骨外转移患者仍能从帕米膦酸盐治疗中获益[24]。在 Kristensen 的研究中,他们观察了口服帕米膦酸盐(4 年,300 mg/ 天)对淋巴结阴性乳腺癌

患者骨转移发生率及总生存率的影响,随访后发现帕米膦酸盐并未能降低这部分患者发生骨转移的风险及提高其总生存率[25]。此外,目前有关伊班膦酸盐抗肿瘤作用的临床试验证据还十分有限。Hoffmann 等学者[26]通过一项小样本的初步研究发现,17 例骨髓弥散肿瘤细胞检测阳性的乳腺癌患者口服伊班膦酸盐(50 mg/ 天)6 个月再次检测骨髓弥散肿瘤细胞时,仅 3 例检测结果阳性,继续服用伊班膦酸盐 6 个月后检测,无一例检测出骨髓弥散肿瘤细胞,提示伊班膦酸盐可以作用于骨髓弥散肿瘤细胞。

2.3 唑来膦酸

唑来膦酸作为第三代双膦酸盐具有更强的抗骨质吸收作用,也被认为是最具潜力用于临床的双膦酸盐。已有的临床证据表明,唑来膦酸具有清除乳腺癌患者骨髓内弥散肿瘤细胞的潜能。乳腺癌患者在接受辅助治疗的同时加用唑来膦酸,其骨髓内的弥散肿瘤细胞有明显减少的趋势[27-29]。唑来膦酸治疗 1 年随访发现其能显著降低骨转移发生率(60%:10%,P=0.0005),该差异可以持续至 18 个月[30]。此外已经有几项针对唑来膦酸辅助治疗乳腺癌的大规模临床试验相继公布了他们的研究结果(见表 1)。ABCSG-12 试验随访 47.8 个月的研究结果发现,对于激素受体阳性的绝经前早期乳腺癌患者,在接受内分泌治疗(他莫昔芬 + 戈舍瑞林或阿那曲唑 + 戈舍瑞林)的同时如果辅以唑来膦酸(4 mg/6 个月)将显著提高治疗效果。患者无瘤生存率提高 3.2%, 疾病进展风险降低 36%, 无复发生存率提高 3.1%,复发风险降低 35%且没有出现新的药物副作用[31]。其随访 62 个月的最新结果显示,联合唑来膦酸治疗的患者 DFS 相比与未联合唑来膦酸治疗的患者仍然具有统计学差异(P=0.009), 而对于死亡风险的影响, 两组间的差异则没有统计学意义(P=0.09)[32]。

Table 1 Ongoing trials of zoledronic acid in breast cancer adjuvant therapy

Trial/year	Patients	Number	Regimen	Dosage of zoledronic acid (ZOL)
ABCSG-12/2010	Stage Ⅰ/Ⅱ Breast Cancer	1803	ZOL/No treatment	4 mg IV every 6 months
Z-FAST/2009	Early breast cancer	602	Immediate ZOL/ Delayed ZOL	4 mg IV every 6 months
ZO-FAST/2009	Early breast cancer	1065	Immediate ZOL/ Delayed ZOL	4 mg IV every 6 months
E-ZO-FAST/2009	Early breast cancer	522	Immediate ZOL/ Delayed ZOL	4 mg IV every 6 months
AZURE/2010	Stage Ⅱ/Ⅲ Breast Cancer	3360	ZOL/No treatment	4 mg IV every 3-4 weeks for 6 doses,then 3 monthly× 8 and 6 monthly× 5

另外进行的全球开放、多中心 Z/ZO/E-ZO-FAST 等试验均是针对不同地区绝经后受体阳性的乳腺癌患者,其报道的研究结果显示绝经后早期乳腺癌患者的辅助治疗中使用唑来膦酸后可以获得无病生存和总生存的优势[33]。此外,仍在进行中的有关早期乳腺癌患者辅助双膦酸盐治疗效果的试验如 BIG-1-04-AZURE 试验(n=3360)将评估高复发风险的早期乳腺癌患者接受标准化疗或内分泌治疗的同时辅以唑来膦酸与单独接受抗肿瘤治疗在无病生存率、无骨转移生存率是否存在差异,试验初步结果不建议乳腺癌患者常规使用唑来膦酸,目前试验正在进一步随访中[34]。SWOG-S0307 试验(n=5400)为一项三期临床随机对照试验,目的是比较三种双膦酸盐(静脉注射唑来膦酸和口服伊班膦酸盐、氯膦酸盐)在抑制早期乳腺癌骨转移方面的效果差异[35]。

尽管目前的研究结果尚未得出一致的结论,相信未来更多大规模的临床试验会真正发掘出双膦酸盐辅助治疗的真正价值。

参 考 文 献(References)

[1] Jemal A, Bray F, Center M M, et al. Global cancer statistics [J]. CA Cancer J Clin, 2011, 61(2): 69-90

[2] Wong M H, Stockler M R, Pavlakis N. Bisphosphonates and other bone agents for breast cancer [J]. Cochrane Database Syst Rev, 2012, 2: CD003474

[3] Russell R G. Bisphosphonates: the first 40 years [J]. Bone, 2011, 49 (1): 2-19

[4] Ebetino F H, Hogan A M, Sun S, et al. The relationship between the chemistry and biological activity of the bisphosphonates [J]. Bone, 2011, 49(1): 20-33

[5] Clezardin P. Potential anticancer properties of bisphosphonates: insights from preclinical studies [J]. Anticancer Agents Med Chem, 2012, 12(2): 102-113

[6] Neville-Webbe H L, Gnant M, Coleman R E. Potential anticancer properties of bisphosphonates[J]. Semin Oncol, 2010, 37 Suppl 1:S53 -65

[7] Aft R. Bisphosphonates in breast cancer: clinical activity and implications of preclinical data [J]. Clin Adv Hematol Oncol, 2011, 9 (3): 194-205

[8] Gnant M. Anticancer activity of bisphosphonates in breast cancer[J]. Anticancer Agents Med Chem, 2012, 12(2): 114-122

[9] Brown H K, Holen I. Anti-tumour effects of bisphosphonates--what have we learned from in vivo models?[J]. Curr Cancer Drug Targets, 2009, 9(7): 807-823

[10] Boissier S, Magnetto S, Frappart L, et al. Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices[J]. Cancer Res, 1997, 57(18): 3890-3894

[11] Boissier S, Ferreras M, Peyruchaud O, et al. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases[J]. Cancer Res, 2000, 60(11): 2949-2954

[12] Aft R. Bisphosphonates in breast cancer: antitumor effects [J]. Clin Adv Hematol Oncol, 2011, 9(4): 292-299

[13] Widler L, Jahnke W, Green J R. The chemistry of bisphosphonates: from antiscaling agents to clinical therapeutics [J]. Anticancer Agents Med Chem, 2012, 12(2): 95-101

[14] Elomaa I, Blomqvist C, Porkka L, et al. Clodronate for osteolytic metastases due to breast cancer [J]. Biomed Pharmacother, 1988, 42 (2): 111-116

[15] Diel I J, Solomayer E F, Costa S D, et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment [J]. N Engl J Med, 1998, 339(6): 357-363

[16] Diel I J, Jaschke A, Solomayer E F, et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up [J]. Ann Oncol, 2008, 19(12): 2007-2011

[17] Saarto T, Blomqvist C, Virkkunen P, et al. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial[J]. J Clin Oncol, 2001, 19(1): 10-17

[18] Saarto T, Vehmanen L, Virkkunen P, et al. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients[J]. Acta Oncol, 2004, 43(7):650-656

[19] Powles T, Paterson A, McCloskey E, et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026] [J]. Breast Cancer Res, 2006, 8(2): R13

[20] Ha T C, Li H. Meta-analysis of clodronate and breast cancer survival [J]. Br J Cancer, 2007 ,96(12): 1796-1801

[21] Paterson A H, Anderson S J, Lembersky B C, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial [J]. Lancet Oncol, 2012, 13(7): 734-742

[22] Conte P F, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial [J]. The Aredia Multinational Cooperative Group. J Clin Oncol, 1996, 14(9): 2552-2559

[23] Kokufu I, Kohno N, Yamamoto M, et al. Adjuvant pamidronate therapy prevents the development of bone metastases in breast cancer patients with four or more positive nodes [J]. Oncol Lett, 2010, 1(2): 247-252

[24] van Holten-Verzantvoort A T, Hermans J, Beex L V, et al. Does supportive pamidronate treatment prevent or delay the first manifestation of bone metastases in breast cancer patients? [J]. Eur J Cancer, 1996, 32A(3): 450-454

[25] Kristensen B, Ejlertsen B, Mouridsen H T, et al. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer[J]. Acta Oncol, 2008, 47(4): 740-746

[26] Hoffmann O, Aktas B, Goldnau C, et al. Effect of ibandronate on disseminated tumor cells in the bone marrow of patients with primary breast cancer: a pilot study[J]. Anticancer Res, 2011, 31(10): 3623-3628

[27] Solomayer E F, Gebauer G, Hirnle P, et al. Influence of zoledronic acid on disseminated tumor cells in primary breast cancer patients[J]. Ann Oncol, 2012, 23(9): 2271-2277

[28] Rack B, Juckstock J, Genss E M, et al. Effect of zoledronate on persisting isolated tumour cells in patients with early breast cancer[J]. Anticancer Res, 2010, 30(5): 1807-1813

[29] Aft R, Naughton M, Trinkaus K, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial [J]. Lancet Oncol, 2010, 11(5): 421-428

[30] Mystakidou K, Katsouda E, Parpa E, et al. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline [J]. Med Oncol, 2005, 22(2): 195-201

[31] Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer [J]. N Engl J Med, 2009, 360(7): 679-691

[32] Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial[J]. Lancet Oncol, 2011, 12(7): 631-641

[33] Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results [J]. Ann Oncol, 2013, 24(2): 398-405

[34] Coleman R E, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid[J]. N Engl J Med, 2011, 365(15): 1396-1405

[35] Gnant M. Zoledronic acid in the treatment of early-stage breast cancer: is there a final verdict?[J] .Curr Oncol Rep, 2012, 14(1): 35-43