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唑来膦酸注射液联合经皮椎体成形术治疗脊柱多发性骨髓瘤的临床疗效*

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摘要 目的：观察脊柱多发性骨髓瘤行唑来膦酸注射液与经皮椎体成形术联合治疗的临床疗效。**方法：**2010年8月至2017年3月，16例行多发性骨髓瘤患者接受经皮椎体成形术与唑来膦酸注射液联合治疗，评定疗效、疼痛缓解及治疗前后血碱性磷酸酶、血清钙、生活质量，记录不良反应。**结果：**(1)疗效：完全缓解1例，部分缓解12例，微小缓解1例，疾病进展1例，无变化1例，总有效率为87.5%(14/16)。(2)疼痛缓解：显效9例，有效6例，无效1例。总有效率93.75%(15/16)。(3)血碱性磷酸酶、血清钙、生活质量：治疗后优于治疗前(P<0.05)。(4)研究期间不良反应轻微。**结论：**脊柱多发性骨髓瘤行唑来膦酸注射液与经皮椎体成形术联合治疗有助于缓解疼痛和改善生活质量。

关键词：多发性骨髓瘤；唑来膦酸；经皮椎体成形术；生活质量
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Clinical Efficacy of Zoledronic Acid injection Combined with Percutaneous Vertebroplasty in the Treatment of Multiple Myeloma of Spine*

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ABSTRACT Objective: To observe the clinical effect of zoledronic acid injection combined with percutaneous vertebroplasty for multiple myeloma of spine. **Methods:** From August 2010 to March 2017, 16 patients with column multiple myeloma underwent percutaneous vertebroplasty combined with zoledronic acid injection. The efficacy, pain relief, blood alkaline phosphatase, serum calcium and quality of life were evaluated before and after treatment, and adverse reactions were recorded. **Results:** Curative effect: complete remission in 1 case, partial remission in 12 cases, minor remission in 1 case, disease progression in 1 case, no change in 1 case, the total effective rate was 87.5% (14/16). (2) Pain relief: 9 cases were markedly effective, 6 cases were effective and 1 case was ineffective. The total effective rate was 93.75% (15/16). Blood alkaline phosphatase, serum calcium and quality of life were better after treatment than before treatment (P<0.05). (5) The adverse reactions were mild during the study. **Conclusion:** Zoledronic acid injection combined with percutaneous vertebroplasty can relieve pain and improve the quality of life in multiple myeloma of spine.

Key words: Multiple myeloma; Zoledronic acid; Percutaneous vertebroplasty; Quality of life
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前言

多发性骨髓瘤(multiple myeloma, MM)是人体浆细胞恶性增殖所致、多发于60岁以上人群、以骨质损害为主要临床特征的一类恶性医学体征，多累及脊柱，其引发的病理性骨折、脊柱失稳、神经根及脊髓受压等病变可导致顽固性腰腿痛，严重者甚至发生截瘫，显著降低生活质量[1-5]。目前针对MM，多在血液科行万珂等药物的化疗治疗，或行放射治疗干预脊柱疼痛，虽可提高MM患者的生存时间，但仅采用单纯的放化疗仍不能改善脊柱多发性骨髓瘤的临床症状，需要外科治疗进行干预[6,7]。目前，对于脊柱多发性骨髓瘤患者，何时行外科手术治疗、术式选择等相关问题仍存在较大的争议，大部分学者认为经皮椎体成形术(percutaneous vertebroplasty，PVP)能缓解脊柱MM患者的临床症状[8-10]。唑来膦酸注射液可改善骨代谢、保护估量的同时，抑制肿瘤的生长[11]。目前国内并无唑来膦酸注射液联合经皮椎体成形术治疗脊柱MM的相关研究。基于此，本研究通过观察两者联合治疗脊柱MM的临床疗效，为脊柱MM的治疗提供理论依据。

1 资料与方法

1.1 一般资料

选取2010年8月至2017年3月就诊于我院、拟行PVP治疗的脊柱MM患者16例，其中，男10例，女6例；年龄(52-83)岁，平均62.5岁；分型：IgM型1例，IgA型5例，IgG型

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9 例,不分泌型 1 例;部位:胸椎骨折 3 例,腰椎骨折 4 例,胸腰椎骨折 9 例; 范围:2 个椎体 2 例,3 个椎体 7 例,4 个椎体 6 例,5 个椎体 1 例。

1.2 纳入与排除标准

1.2.1 纳入标准 (1)诊断满足《中国多发性骨髓瘤诊治指南·2017 年版》[12],且经免疫固定和血清蛋白电泳、骨髓细胞学检查进一步确诊为脊柱 MM;(2)术前经影像学(X 线、CT、RMI)检查确定 2 个以上椎体骨折(椎体后壁完整),规范放疗、干扰素、M2 化疗疗效欠佳,拟行 PVP 治疗;(3)卡氏评分不低于 40 分,且预计生存期 90 天以上;(4)对研究知情并签署同意书者。

1.2.2 排除标准 (1)近 1 月内服用双膦酸盐类药或对该药过敏者;(2)腰椎间盘突出、腰椎管狭窄、椎体滑脱等明显异常或血液病、内分泌病、电解质经常紊乱者;(3)孕妇,哺乳期妇女及合并 MM 以外其它严重危及生命基础病者。

1.3 治疗方法

均接受 PVP 联合唑来膦酸注射液治疗。PVP 步骤:患者俯卧,C 臂 X 线机定位患椎,消毒后逐层浸润麻醉,于棘突旁(2-3)厘米进针, 经椎弓根入路穿刺, 确保穿刺针尖位于患椎前 1/3 时,拔出针芯,侧位透视辅助下,将预先配制的呈糊状的骨水泥(聚甲基丙烯酸甲酯)打入椎体,严防骨水泥外漏,胸、腰椎骨水泥用量平均 2.5、4.5 毫升, 手术由同一高年资主任医师主刀完成。术后(3-5)天卧床,之后胸腰部支具辅助下逐步增加活动。唑来膦酸注射液 (规格:100 毫升:5 毫克 / 瓶; 批准文号:H20120204;厂家:Novartis Pharma Schweiz AG)4 毫克溶于 100 毫升 0.9%氯化钠注射液中, 经静脉用药, 每次滴注不低于 15 分钟,1 次 / 月,规范应用 3 个月。定期复查血常规、肝肾功能及 X 线等。

1.4 观察指标

1.4.1 疗效 参照国际通用欧洲骨髓移植协作组制定的标准[13],分为无变化(unchanged,NC)、进展(progression of disease,PD)、微小缓解 (minor remission,MR)、部分缓解 (partial remission,PR)、完全缓解 (complete remission,CR), 其中, 总有效率 = (MR+PR+CR)/ (NC+PD+MR+PR+CR) × 100%。

1.4.2 疼痛缓解及治疗前后血碱性磷酸酶(ALP)、血清钙(Ca^{2+})、生活质量 (1)疼痛分级参照世界卫生组织提出的标准[14],无疼痛为 0 级;疼痛轻微,无用药时可忍受者为Ⅰ级;中度疼痛,需通过一般止痛药方可正常睡眠者为Ⅱ级;重度疼痛,需应用麻醉药才能正常睡眠者为Ⅲ级。疼痛缓解不低于 2 个级别者为显效,疼痛缓解 1 个级别者为有效,疼痛无缓解或反而加重者为无效。总有效率 =1－无效率。(2)血 ALP、Ca^{2+} 测定方法:取晨起、空腹 8 小时、安静状态肘静脉血 2 管,3 毫升 / 管, 离心(4000 转 / 分钟,10 分钟)后取上清液,置于零下 70 摄氏度的冰箱中备用。ALP、Ca^{2+} 采用酶联免疫吸附法经全自动生化分析仪检测,步骤分别按照上海钰博生物科技有限公司、上海双赢生物科技有限公司提供的试剂盒操作说明进行[3] 生活质量评估参照肿瘤患者生活质量评分[15],包括面部表情、日常生活、对 MM 的认识、同事的配合与理解、疼痛、疲乏、睡眠、精神、食欲等 12 个维度,每个维度 5 个匹配条目(对应分值 1-5 分),总积分(0-60)分,分值越高,提示生活质量越好。

1.4.3 不良反应 包括手术(骨水泥渗漏等)、唑来膦酸(过敏、中毒等)相关不良反应。

1.5 统计学处理

统计学分析经 SPSS20.0 完成,ALP 等计量资料用(均数±标准差)表示,治疗前后比较采用配对 t 检验,$P<0.05$ 时,则表示有统计学差异性。

2 结果

2.1 疗效

CR 1 例,PR 12 例,MR 1 例,PD 1 例,NC 1 例, 总有效率为 87.5%(14/16)。

2.2 疼痛缓解

显效 9 例,有效 6 例,无效 1 例。总有效率 93.75%(15/16)。

2.3 治疗前后 ALP、Ca^{2+}、生活质量对比情况

16 例患者治疗后 ALP、Ca^{2+} 低于治疗前($P<0.05$),治疗后生活质量评分高于治疗前($P<0.05$),见表 1。

表 1 两组治疗前后 ALP、Ca^{2+}、生活质量对比情况

Table 1 The comparison of ALP, Ca^{2+} and quality of life before and after treatment between the two groups

Point of time	Cases	ALP(IU/L)	Ca^{2+}(mmol/L)	Quality of Life Score (Score)
Before treatment	16	235.16± 51.07	4.56± 0.92	21.06± 5.24
After treatment	16	88.01± 10.22	3.51± 0.81	42.06± 7.39
t		16.255	8.221	11.255
P		0.000	0.028	0.007

2.4 不良反应

复查见骨水泥椎间隙渗漏 2 例,椎旁渗漏 3 例,患者无临床异常。2 例出现发热,最高 3.85℃;2 例出现恶心反应,无呕吐;1 例出现全血细胞减少;2 例因低钙血症发生肌肉痉挛、酸痛;1 例出现轻度肾功能异常。给予观察或对症处理后均有效缓解。

3 讨论

随着国民生活水平的提高和人均寿命的延长,我国已提前进入不可逆的老龄化社会阶段, 而未来 20 年超过七成的新发肿瘤患者均为老年人。MM 是在血液系统中发生率、死亡率分别约为 10%、20%, 对老年人身心健康影响不容忽视的一种恶性肿瘤[16-18]。MM 病理研究显示[19-23],患者体内浆细胞持续增殖的同时,还分泌大量的单克隆免疫球蛋白、M 蛋白、破骨细胞活化因子(白介素、肿瘤坏死因子)等物质,通过抑制成骨、促进破骨而打破骨代谢平衡,导致病理性骨折、高钙血症、脊髓压迫、

骨痛等溶骨性事件,其骨质损害率约(70%-95%),已引起骨科领域同仁的广泛关注。脊柱 MM 在局部膨胀、浸润生长可对神经末梢、神经根产生强烈的刺激;而椎体病理性骨折的发生破坏了脊柱的力学平衡,这均可导致显著疼痛,影响正常生活。PVP 是经穿刺器械及特定输送管道将骨水泥打入椎体,其治疗原理为[24,25]:(1)聚甲基丙烯酸甲酯具有一定细胞毒性,且固化过程中可产生较为可观的热效应,这既能杀灭瘤细胞,又可使局部神经等组织发生坏死,降低机体感觉的敏感性,从而直接止痛。(2)骨水泥可固定局部骨折,恢复椎体高度,有助于改善后凸畸形、提高脊柱稳定性、减缓相邻节段退变,从而间接止痛。(3) 椎体内的骨小梁与骨水泥相互交错对预防骨折意义重大。以上显示了 PVP 对 MM 所致椎体病理性骨折的防治作用。

另外,国际骨髓瘤工作组一致认为,所有需接受抗骨髓瘤治疗的 MM 患者,无论骨质状况如何,均建议使用二膦酸盐类药控制,唑来膦酸是该类药物中的第三代,其治疗 MM 的作用机制有[26]:(1)通过下调 CD138 的表达,进而对 MM 患者 KM3 细胞的增值发挥抑制作用。(2)通过尿液加速磷、钙排泄,从而降低 MM 引发的高钙血症。(3)通过抑制白介素、肿瘤坏死因子等炎性因子进而减轻局部炎症及溶骨过程。(4)不仅可抑制破骨细胞活性及 MM 患者体内蛋白异戊烯化,而且对该细胞凋亡有显著促进作用,其抗骨吸收功效约是帕米膦酸 200 倍,可大大降低溶骨性事件发生的危险度。(5)对肿瘤细胞粘附、浸润骨基质的过程及肿瘤内部及附近血管的生长有显著抑制作用。本研究 16 例患者治疗后发现,总有效率约 88%,疼痛缓解率 94%,ALP、Ca^{2+}、生活质量较治疗前显著改变(P<0.05),与 Rosen 等[27]在乳腺癌研究的观点吻合,提示放化疗效果欠佳的脊柱 MM 行唑来膦酸注射液与 PVP 联合治疗有助于缓解疼痛、改善生活质量。

在不良反应上,本研究 PVP 术后骨水泥渗漏未表现出不适,对此,笔者有以下心得分享:(1)术前结合影像学资料严格把握手术适应症,排除椎体后缘破坏严重者。(2)术中穿刺透视时,当针尖到达骨皮质及进针还未超过椎弓根前缘的过程中,应确保穿刺针尖居于椎弓根 " 猫眼 " 内侧(正位);当针尖刺透骨皮质逐渐向椎体进入时,在脊柱侧位透视辅助下,用外科锤将穿刺针打入椎体,至针尖位于椎体前 1/3 处,此时已超过 " 猫眼 " 内侧(正位);(3)骨质疏松性椎体骨折胸、腰椎打入骨水泥推荐用量分别为 3、5 毫升,笔者认为病理性骨折骨质损害严重,打入过程应紧密透视,本研究胸腰椎打入量均值为 2.5、4.5 毫升,建议稍小于常规骨水泥用量。另外,唑来膦酸主要经肾脏以原型排出体外,剂量过大和长期使用,可降低损伤肾功能,甚至急性肾小管坏死;唑来膦酸使用后 5 天,约 35%的患者有轻度发热,与用药剂量及个体耐受有关,与本研究一致。Wang 等[28]认为,造血因子、细胞外基质、骨髓基质细胞共同构成骨髓微环境,该环境是造血干细胞发育、生存、定居的场地,骨髓基质细胞通过旁分泌、直接分泌等形式对骨髓瘤及其它内分泌细胞产生活化作用,从而增加此环境中基质降解酶、血管因子含量,最终对骨髓瘤的增殖和迁移发挥促进作用。唑来磷酸在发挥抗 MM 效应的同时,还可抑制骨髓基质细胞产生血小板,与本研究并不矛盾。此外,曾有报道指出[29,30],唑来膦酸还可导致下颌骨坏死、房颤、食道癌、视觉异常、继续行甲旁亢等异常,而糖皮质激素又可通过杀伤骨髓 B 淋巴细胞(浆细胞来源)进而提高 MM 治疗效果,这均有待于进一步临床研究验证。

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