

doi: 10.13241/j.cnki.pmb.2014.26.018

PAD 方案治疗 75 例初诊多发性骨髓瘤疗效观察*

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摘要 目的: PAD 方案已成为目前多发性骨髓瘤(MM)治疗的一线方案,国内外就其疗效和不良反应发生均有报道,本实验旨在观察并探讨 PAD 方案治疗我中心初诊多发性骨髓瘤患者的疗效和不良反应,为临床工作提供参考。**方法:** 我科 75 例初诊多发性骨髓瘤患者给予 PAD 方案 4-6 疗程,评估疗效及不良反应。**结果:** 75 例患者接受 PAD 方案化疗,四疗程后总有效率(CR+VGPR+PR)为 73.3%,其中 CR 5 例,占 6.7%,VGPR 12 例,占 16%,PR 38 例,占 50.7%;无效例数为 20 例,占 26.7%,其中 SD 17 例,占 22.7%,PD 3 例,占 4%;1 年总生存率为 75%,2 年总生存率为 62.7%。血液学不良反应有白细胞降低 34 例(45.3%),血小板降低 10 例(13.3%);非血液学不良反应有周围神经系统症状 25 例(33.3%),疱疹病毒感染 7 例(9.3%),消化系统症状 15 例(20%),乏力 14 例(18.7%),呼吸系统症状 29 例(38.7%),激素相关症状 3 例(4%)。绝大部分患者可以耐受且完成相应化疗疗程。**结论:** 我中心 PAD 方案疗效令人满意,不良反应可耐受,同国内外报道的疗效反应率相近,不良反应发生率更低,是治疗多发性骨髓瘤的首选方案。

关键词: 多发性骨髓瘤;硼替佐米;阿霉素;地塞米松;疗效

中图分类号: R733.3 **文献标识码:** A **文章编号:** 1673-6273(2014)26-5072-03

Efficacy Evaluation of PAD Regimen for the Patients with Newly Diagnosed Multiple Myeloma*

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ABSTRACT Objective: PAD regimen has become the first-line therapy of multiple myeloma (MM), and scientists all over the world have reported its efficacy and adverse reactions. This study aimed to investigate and explore the efficacy and adverse reactions of PAD regimen in patients with newly diagnosed multiple myeloma in our center, and to provide reference for clinical work. **Methods:** 75 patients with newly diagnosed multiple myeloma in our department were treated with 4-6 PAD treatment program. The efficacy and adverse reactions were evaluated. **Results:** After PAD regimen treatment for 4 courses, the overall response rate (CR + VGPR + PR) was 73.3%, including 5 cases of complete response (6.7%), 12 cases of good partial response (16%), 38 cases of partial response (50.7%); There were 20 invalid cases (26.7%), including 17 cases of SD (22.7%) and 3 cases of PD (4%); overall survival rate of one year was 75%, and the overall survival rate of two years was 62.7%. Hematologic adverse reactions included 34 cases of leukopenia (45.3%), 10 cases of thrombocytopenia (13.3%); non-hematologic adverse reactions included 25 cases of peripheral nervous system symptoms (33.3%), 7 cases of herpes virus infection (9.3%), 15 cases of digestive symptoms (20%), 14 cases of fatigue (18.7%), 29 cases of respiratory symptoms (38.7%), 3 cases of hormone-related symptomst(4%). The majority of patients were able to tolerate and complete the chemotherapy. **Conclusion:** The efficacy of PAD regiment in our center was satisfactory, and the adverse reactions could be tolerated, and compared with reports at home and abroad, we had the same efficacy and less adverse reactions. so it was the first choice in the treatment of multiple myeloma.

Key words: Multiple myelom; Bortezomib; Doxorubicin; Dexamethasone; Efficacy

Chinese Library Classification: R733.3 **Document code:** A

Article ID: 1673-6273(2014)26-5072-03

前言

多发性骨髓瘤是起源于浆细胞的血液系统恶性肿瘤,在血液系统肿瘤中其发病率仅次于非霍奇金淋巴瘤,至今仍然被认为无法治愈。据统计,截止到 2014 年,仅美国就有大约 60000

个确诊多发性骨髓瘤的患者,且以每年 23000 人次递增^[1]。目前多发性骨髓瘤的治疗仍然以化疗为主,使用经典的化疗方案如 VAD、TAD 等,患者的中位生存期大约为 2-3 年,疗效不甚满意,自体干细胞移植虽然可以延长患者生存期,但是绝大部分患者仍然复发或者进展到难治性 MM,因此急待更为有效且耐

* 基金项目:国家自然科学基金项目(81172247)

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(收稿日期:2014-03-19 接受日期:2014-04-15)

受性良好的新型抗 MM 药物的出现^[23]。硼替佐米为新型的蛋白酶抑制剂,于 2008 年获 FDA 批准用于治疗多发性骨髓瘤,并呈现了其良好的抗骨髓瘤细胞效应,而且硼替佐米联合阿霉素的疗效更优于单用硼替佐米^[4]。目前临床使用硼替佐米联合阿霉素和地塞米松的 PAD 方案作为多发性骨髓瘤一线方案,其疗效和传统的 VAD 方案(长春新碱联合多柔吡星和地塞米松)、DVD 方案(脂质体多柔吡星联合长春新碱加地塞米松)以及 MP 方案(美法仑联合泼尼松)相比具有更高的 CR 率以及更少的不良反应发生率,且绝大多数不良反应可耐受^[5],为了解 PAD 方案治疗多发性骨髓瘤的疗效反应性及药物不良反应,现评估了我中心 2010 年-2012 年 75 例初诊的多发性骨髓瘤患者,结果整理如下。

1 资料与方法

1.1 一般资料

入组患者为 2006 年 1 月到 2012 年 9 月收治我科的初诊的 75 例多发性骨髓瘤患者,男性 55 例,女性 20 例;中位年龄 56 岁(22-80 岁);其中 IgG 型 37 例,IgA 型 14 例,IgM 型 1 例, λ 轻链型 8 例, κ 轻链型 10 例,不分泌型 5 例。根据 D-S 分期系统,II 期 13 例,III 期 62 例;根据 ISS 分期系统,I 期 2 例,II 期 23 例,III 期 50 例。

1.2 治疗方法

入组患者均给予 PAD 方案化疗,其中硼替佐米按 1.3 mg/m² 于第 1、4、8、11 天静脉注射,阿霉素按 10 mg/m² 于第 1-4 天静脉注射,地塞米松 40 mg 于第 1-4 天静脉滴注。给药期间监测各项指标,若出现 II 级以上不良反应则推迟用药。

1.3 疗效以及不良反应评估

入组患者的疗效评估参照国际骨髓瘤工作组(IMWG)疗效标准:①完全缓解(CR):无克隆性血清 M 蛋白;②非常好的部分缓解(VGPR):血清 M 蛋白下降 $\geq 90\%$;③部分缓解(PR):血清 M 蛋白下降在 50%~90%之间;④疾病稳定(SD):不符合 CR、VGPR、PR 和 PD 的标准;⑤疾病进展(PD):血清 M 蛋白增加 $\geq 25\%$ 。本实验中有效包含 CR、VGPR 和 PR,无效包含 SD 和 PD。不良反应根据 NCI CTCAEv3.0 标准,每天评价并记录。

2 结果

2.1 疗效评估

入组的 75 例患者均接受 4-6 疗程的化疗,为统一评估疗效,在 4 疗程结束后按 IMWG 疗效标准评估。总有效例数(CR+VGPR+PR)为 55 例,总有效率 73.3%,其中 CR 5(6.7%)例,VGPR 12(16%)例,PR 38(50.7%)例;无效例数 20(26.7%)例,其中 SD 17(22.7%)例,PD 3(4%)例(表 1)。入组患者中,1 年总生存率 75%,2 年总生存率 62.7%。

表 1 75 例初诊 MM 患者 PAD 方案 4 疗程后疗效

Table 1 The efficacy of 4 courses of PAD regimen in 75 patients with newly diagnosed MM

Efficacy	CR	VGPR	PR	SD	PD	CR+VGPR+PR
Cases	5(6.7%)	12(16%)	38(50.7%)	17(22.7%)	3(4%)	55(73.3%)

2.2 血液学不良反应

化疗过程中共有 34(45.3%)例患者出现白细胞降低,其中 I 级 4(5.3%)例,II 级 16(21.3%)例,III 级 14(18.7%)例,III 级患者给予粒细胞集落刺激因子及抗生素预防感染,其余停药后

均能恢复,可以完成化疗;10(13.3%)例患者出现血小板减少,其中 II 级 2(2.7%)例,III 级 8(10.7%)例,给予输注血小板及停药治疗,均能恢复并完成化疗(表 2)。

表 2 血液学不良反应

Table 2 Hematologic adverse reactions

Level	I	II	III	Total
Leukopenia	4(5.3%)	16(21.3%)	14(18.7%)	34(45.3%)
Thrombocytopenia	0	2(2.7%)	8(10.7%)	10(13.3%)

2.3 非血液学不良反应

75 例患者在化疗期间,部分出现不同程度的非血液学不良反应,其中出现周围神经症状 25(33.3%)例,疱疹病毒感染 7(9.3%)例,恶心呕吐、腹胀腹泻便秘等消化系统非特异性症状 15(20%)例,乏力 14(18.7%)例,上感及肺炎等呼吸系统症状

29(38.7%)例,激素使用相关症状如血糖升高 1(1.3%)例、低钾血症 2(2.7%)例,静脉血栓形成无(表 3)。其中,2 例出现周围神经系统症状患者因无法耐受而中断治疗,2 例因肺部感染肺炎救治无效死亡,其余患者经对症支持治疗,均可以耐受而完成相应化疗疗程。

表 3 非血液学不良反应

Table 3 Non-hematologic adverse reactions

Non-hematologic adverse reactions	Cases	Non-hematologic adverse reactions	Cases
Peripheral nervous system symptoms	25(33.3%)	Herpes virus infection	7(9.3%)
Digestive symptoms	15(20%)	Fatigue	14(18.7%)
Respiratory symptoms	29(38.7%)	Hormone -related symptoms	3(4%)

3 讨论

硼替佐米自从上市以来,以其良好的疗效,取代传统方案成为目前治疗多发性骨髓瘤的一线方案。硼替佐米属于蛋白酶体抑制剂,其通过抑制 Ik B 的大量降解来上调 Ik B, Ik B 和 NF- κ B 的结合可以有效抑制骨髓瘤细胞中的 NF- κ B 表达,使细胞增殖基因表达受抑制,达到抗骨髓瘤的作用, NF- κ B 的表达和 MM 细胞的 IL-6 分泌相关, NF- κ B 活性的抑制也可以抑制 MM 细胞的 IL-6 分泌,从而干扰骨髓基质细胞和 MM 细胞的相互作用达到从骨髓微环境角度治疗多发性骨髓瘤的目的^[6-8]。而且硼替佐米与多种抗肿瘤药物如阿霉素有协同抗骨髓瘤细胞的作用^[9]。研究表明,小剂量硼替佐米通过上调 P16 蛋白的表达来诱导骨髓瘤细胞的衰老^[10],这也为临床治疗多发性骨髓瘤提供了新的思路。

多发性骨髓瘤至今被认为是一种无法治愈的疾病,传统方案如 VAD、TAD、MP 方案等疗效均不尽人意,总有效率难以超过 50%,相对于传统化疗方案,多项研究均证明硼替佐米联合阿霉素和地塞米松的 PAD 方案具有更好的疗效。一项 PAD 方案治疗 64 例患者的研究显示,67%患者达到了 PR 以上的疗效,包括 25%的 VGPR 和 CR 反应率,一年生存率达到 66%^[11]。另外一项 II 期临床实验研究表明, PAD 方案治疗 MM 相对于传统方案来讲可以明显提高患者的 CR 率^[12]。同样,另外两项研究表明对于初发和复发难治的多发性骨髓瘤患者,使用 PAD 方案可以获得更好的反应性和延长无病生存期^[13,14]。本研究结果显示,我中心 75 例初诊多发性骨髓瘤,使用 PAD 作为一线方案,总有效率达 73.3%, VGPR 以上疗效达 22.7%, 1 年总生存率达 75%。硼替佐米联合阿霉素及地塞米松的 PAD 方案显示了其良好的抗 MM 效应。

同时,对于 PAD 方案的副反应发生情况,越来越多的文献报道硼替佐米的副作用主要为血小板减少、周围神经炎、乏力及胃肠道反应^[15-18]。其中周围神经系统症状为 PAD 方案所特有,相比于传统方案, PAD 并未降低副作用发生率,相反其副反应发生情况更应受到重视,但大多数患者可以耐受。国外研究报道,硼替佐米治疗复发或者难治的 MM 患者,仍然有着较好的反应性,且不良反应可以耐受^[19,20]。我中心患者主要的血液学不良反应为白细胞降低,发生率为 45.3%,均为 III 级以下,给予相应对症治疗,可以继续完成化疗。另有 10 例患者出现 III 级以上血小板降低。本研究中的非血液学不良反应主要有周围神经系统症状(33.3%), 疱疹病毒感染(9.3%), 消化系统非特异性症状(20%), 乏力(18.7%), 上感及肺炎等呼吸系统症状(38.7%), 激素使用相关症状如血糖升高(1.3%)、低钾血症(2.7%), 除 2 例因严重的肺部感染死亡,其余经停药后对症治疗均好转,绝大部分均可完成化疗。

综上所述,硼替佐米联合阿霉素及地塞米松的 PAD 方案作为治疗多发性骨髓瘤的一线方案,可以明显提高患者疗效反应性,延长无病生存期,其安全性和有效性有多方证据作为支持;不良反应发生情况基本同传统化疗方案,经过对症支持治疗,患者耐受性良好,是多发性骨髓瘤患者的首选。本研究着重阐述我中心初诊的 MM 患者对于 PAD 方案的疗效情况以及和国内外报道相比较,为以后的临床诊疗工作提供参考。硼替

佐米作为一种新型的蛋白酶体抑制剂用于 MM 的一线治疗,其具体的抗 MM 机制还有待于进一步研究,硼替佐米为主的 PAD 方案治疗难治复发的 MM 患者的疗效也有待于进一步的观察。

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