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负载自体热休克凋亡癌细胞抗原的DC治疗三阴性乳腺癌的随机对照多中心临床试验

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摘要：

评价自体热休克凋亡肿瘤细胞抗原负载DC对Ⅰ到Ⅳ期ER、PR、Her2三阴性乳腺癌（triple-negative breast cancer, TNBC）患者治疗的疗效和患者对该治疗的耐受性。方法：入选南京、常州、无锡三地3个医院的TNBC患者168例，按照2∶1的比例使用随机数字表将患者随机分组为DC免疫组112例、对照组56例。DC疫苗治疗每周1次，4次为1个疗程，疗程间间隔1个月，共3个疗程。疫苗治疗前、后检测患者外周血中细胞因子谱（IL-2、IL-10、IL-12、TNF-α和IFN-γ）水平和肿瘤特异性CD8+IFNγ+T细胞比例以及进行DTH试验。末次治疗后每3个月随访1次，随访2年，统计患者疾病无进展生存率（PFSR）。结果：Ⅰ~Ⅲ期TNBC患者DC免疫治疗1个疗程后，IL-2、TNF-α和IFN-γ水平即较治疗前（基线）显著升高（PIL-2=0.038 4、PTNF-α=0 023 7、PIFN-γ=0.022 1），且随疗程增加其水平不断升高；而Ⅳ期TNBC患者治疗3个疗程后细胞因子水平均无明显提高。Ⅰ~Ⅲ期TNBC患者外周血CD8+IFN-γ+T细胞比例提升速度与幅度较为缓慢，3个疗程后提升幅度才显示有统计学意义（P<0.05）。患者的DTH试验阳性率伴随疗程数的增加而提升，两者呈正相关关系（r=0.973）；早期（Ⅰ期和Ⅱ期）TNBC患者DTH平均阳性率明显高于中晚期患者（Ⅲ期和Ⅳ期）。2年随访期内Ⅰ~Ⅱ期TNBC患者病情均较稳定，生存率100%；Ⅲ~Ⅳ期TNBC患者DC治疗组PFSR明显高于对照组（71.43% vs 32.73%，P<0.05）。Ⅰ~Ⅳ期DTH阳性患者的PFSR明显高于DTH阴性患者（87.30% vs 51.02%，P<0.05）。治疗组112例TNBC患者对DC治疗耐受良好，未发现Ⅱ级以上不良反应。结论：自体热休克凋亡肿瘤细胞抗原负载DC可有效诱导早期TNBC患者产生Th1型免疫应答反应，分泌高水平Th1型抗瘤因子，3个疗程后可激发明显的肿瘤抗原特异性CTL反应，DTH试验可作为DC免疫有效性的评价指标之一。该DC免疫治疗方法可抑制晚期TNBC患者疾病进展，从而提高PFSR，患者耐受性良好。

关键词：三阴性乳腺癌 树突状细胞 疫苗 免疫治疗 随机对照试验

Outcomes of patients with triple-negative breast cancer after vaccination with autologous dendritic cells loaded with apoptotic heat-shocked tumor antigen: Results from an multicenter randomized controlled clinical trial

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Abstract:

To assess the efficacy and safety profiles of vaccination with autologous DC loaded with apoptotic heat-shocked autologous tumor cell antigens in the treatment of triple-negative breast cancer (TNBC). Methods: A total of 168 patients with TNBC were recruited from three hospitals located, respectively, in Nanjing, Changzhou and Wuxi and randomized to a control group (n=56) and a treatment group (n=112). Patients in the treatment group were treated with DC vaccination for three cycles (one week each at an interval of one month) whereas those in the control group received placebo. The primary outcome measures were disease progression time (DPT) and progression-free survival rate (PFSR) at the end of 2-year follow up. The secondary outcome measures were side effects, tolerance to DC vaccination, tumor specific immune responses (i.e., changes in IL-2, IL-10, IL-12, TNF-α and IFN-γ concentrations), the percentage of specific CD8+IFN-γ+T lymphocytes in peripheral blood and delayed type Ⅳ hypersensitivity reaction (DTH) before and after DC vaccinations. Results: No more than level Ⅱ side effects were observed in any of the participants. After one cycle of vaccination, there were significant and sustained increases in serum levels of Th1 type cytokines IL-2 (P=0 038), TNF-α (P=0.024) and IFN-γ (P=0.022) in patients with stage I to stage Ⅲ lesions. The number of tumor-specific CD8+IFN-γ+T lymphocytes in the peripheral blood was increasing slowly and gradually over the course of vaccination therapy in patients with stage I to stage Ⅲ lesions; by the third cycle of DC vaccination the number became significantly higher as compared with the placebo (P<0.05). Overall, the rate of DTH was positively correlated with the vaccination cycle (r=0.973, P<0.05). When disease stages were compared, the rate of DTH was significantly higher in patients with stage I to stage Ⅲ disease than that in patients with stage Ⅳ lesions. The average DPT was 669 days in patients with stage Ⅰ to stage Ⅲ lesions and 656 days in stage Ⅳ patients in the treatment group, significantly longer than that in patients with stage I to stage Ⅲ (618 days) and stage Ⅳ (573 days) lesions in the control group (P<0.001). The average PFSR of stage Ⅲ and stage Ⅳ patients was 71.43% in the treatment group, but only 32.73% in the corresponding patients in the control group (P<0.001). Moreover, the average PFSR of DTH-positive patients was 87.30%, significantly higher than that of DTH-negative patients (51.02%). Conclusion: Autologous DC loaded with heat-shocked apoptotic autologous tumor cells may be effective in both eliciting the non-specific immune response of Th1 cells and tumor-specific CTL responses and delaying disease progression and improving survival in triple-negative breast cancer patients.

Keywords:triple-negative breast cancer dendritic cell vaccination immunotherapy randomized controlled trial

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