

诊疗经验

两性霉素 B 治疗血液恶性肿瘤患者肺部真菌感染的临床观察

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血液恶性肿瘤患者化疗后侵袭性真菌感染(invasive fungal infection, IFI)的发病率非常高^[1,2],在强力抗生素(碳青霉烯类及万古霉素)治疗4~7 d后,患者仍中、高热不退,肺部CT提示感染病灶的进展,此时,经验性抗真菌治疗十分必要^[2]。十多年来,我们常首先使用静脉滴注伊曲康唑、伏立康唑、米卡芬净、卡泊芬净等药物,但是费用高。近一年,我们观察了国产两性霉素B在急性白血病、淋巴瘤、多发性骨髓瘤患者肺部真菌感染治疗中的疗效和不良反应,报道如下。

临床资料

一般资料 选择2019年10月至2021年8月在运城市中心医院血液内科住院的13例患者(男6例,女7例),年龄49~74岁,平均58岁。基础疾病:急性粒细胞白血病5例,急性淋巴细胞白血病1例,弥漫大B细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)3例,外周T细胞淋巴瘤1例,多发性骨髓瘤3例。13例分别根据我国白血病、淋巴瘤、多发性骨髓瘤诊断和治疗指南,接受了联合化疗方案治疗1~5个疗程,化疗后患者中性粒细胞减少,其中8例中性粒细胞缺乏,出现发热、咳嗽,13例均经验性静脉注射广谱抗生素治疗4~7 d无效,肺部CT感染性病灶扩大或出现新感染影,其中2例半乳甘露聚糖检测实验阳性。根据我国“血液病/恶性肿瘤患者侵袭性真菌感染的诊断标准与治疗原则(第6版修订版)”^[2],其中11例为经验治疗,2例为诊断驱动治疗。给予两性霉素B(欧泊,华北制药产,批号:国药准字H13020284,规格5mg)静脉滴注治疗,此观察经医院伦理委员会审批通过,患者知情并签署同意书。

两性霉素B治疗方法及不良反应的防治 首日两性霉素B 5 mg,第2天10 mg,第3天开始,每日25 mg,加入5%葡萄糖500 mL中,缓慢静脉滴注,9~10滴/min,滴注12 h以上(缓慢滴注是避免发热、寒颤的关键),持续用药至患者体温正常后10 d或临床症状好转且肺部CT显示炎症明显好转后1周停药。密切观察有无畏寒、寒战、发热。治疗开始头2~3 d,滴注前给予地塞米松3 mg 静脉注射。注意预防低钾血症,口服10%氯化钾10 mL/次,3次/d,或氯化钾缓释剂。血钾低者,每天再静脉补钾2~3 g。观察尿常规,每2天查血尿素氮、肌酐水平,注意肾损害,尤其在静脉滴注用药5 d后。另外,观察心电图、肝功能、周围神经炎、恶心、呕吐的情况。

疗效评价 根据我国侵袭性真菌病治疗疗效评估标准^[2],比较两性霉素B治疗前、治疗7~10 d后、治疗20 d后患者的临床症状、体征、肺部CT感染灶吸收情况,治疗有效需包括^[2,3]:经验治疗或诊断驱动治疗,在开始两性霉素B治疗至停药后7 d无新发真菌感染;治疗后无发热;治疗后未因药物副作用或缺乏疗效停药;治疗后肺部CT病灶直径缩小25%以上。

结 果

疗效 2例半乳甘露聚糖检测实验阳性,且肺部CT呈曲霉菌感染相关的影像学表现(伴晕征的较致密、边界较清楚的感染灶,实变病灶中出现新月征各1例),治疗10 d后病灶明显改善;治疗20 d,肺部CT病灶全部吸收。11例经验性治疗者中,仅1例多发性骨髓瘤患者和1例复发难治性DLBCL患者在两性霉素B治疗7~10 d临床症状和肺部CT表现无改善外,其余9例均获有效:在两性霉素B治疗5~7 d后均退热,治疗10 d后肺部CT感染病

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灶明显吸收,缩小 50% 以上,见图 1、2,且无新发真菌感染,停药 7 d 后仍无新的感染。

两性霉素 B 的不良反应 13 例两性霉素 B 最少用药时间 7 d,最多用药时间 25 d,多数用药时间 12 ~ 17 d。其中仅 1 例在静脉滴注第 3 天出现畏寒、发热 38.7℃ 外,余均未出现明显发热。在每天常规口服补钾 3 ~ 4 g 治疗下,有 3 例血钾仍低于 3.1 mmol/L,最低者为 2.7 mmol/L,经静脉补钾 4.5 g/d,血钾水平逐渐恢复。肾功能受损 1 例,在用药第 9 天后出现多尿,尿比重减低,2 d 后血肌酐 134 μ mol/L,停药 5 d 后恢复正常。3 例轻度恶心、纳差。

讨 论

侵袭性真菌病(invasive fungal disease, IFD)在急性白血病化疗后的发生率非常高。有研究(China assessment of antifungal therapy in hematological disease study, CAESAR 研究)显示^[4],血液恶性肿瘤患者化疗中,确诊和临床诊断 IFD 总发生率为 2.1%,其中急性髓细胞白血病 IFD 发生率最高,特别在诱导化疗期间。对气道传播为主的真菌病原菌如曲霉菌和毛霉菌多累及肺部,影像学检查尤其是高分辨 CT 检查具有重要临床诊断意义^[5]。国内外以化疗后持续粒细胞缺乏伴发热,广谱抗菌药物治疗 4 ~

7 d 无效,作为启动经验抗真菌治疗的主要依据,适用于 IFD 高危患者^[2,6,7]。经验性抗真菌治疗药物一般选择覆盖曲霉菌的广谱抗真菌药物,包括卡泊芬净、脂质体两性霉素 B、两性霉素 B、米卡芬净和伏立康唑等^[2],我们选用了国产两性霉素 B。急性白血病和血液肿瘤患者面临多次化疗,经济压力比较大,两性霉素 B 是我国抗真菌治疗指南中推荐应用于经验性治疗和诊断驱动治疗播散性念珠菌病、侵袭性曲霉病的药物^[2],又是进入国家医保甲类药品且价格最为便宜的一种,我们实践体会,只要肾功能正常,认真防治不良反应,应用两性霉素 B 能很好的控制肺部真菌感染,其疗效确定且性价比高。

两性霉素 B 被认为“毒性较大,可有发热,寒战”^[8],我们体会,只要体表面积、体重不是过大,每天 25 ~ 30 mg 静脉滴注超过 12 h,治疗效果很好,且能避免寒战、高热。Eriksson 等报道^[9],两性霉素 B 在 24 h 内缓慢静脉滴注的疗效与 4 h 快速滴注的疗效相同,但明显减少寒战、发热。同一位患者一天 25 mg 剂量在 8 h 内滴注完均会发生高热,而改为 12 h 滴完,就无寒战、高热。使用两性霉素 B 容易出现低钾血症(肾小管功能受损),一定要注意防治,也可避免心律失常。预防性补充钾盐,监测血液电解质十分重要。

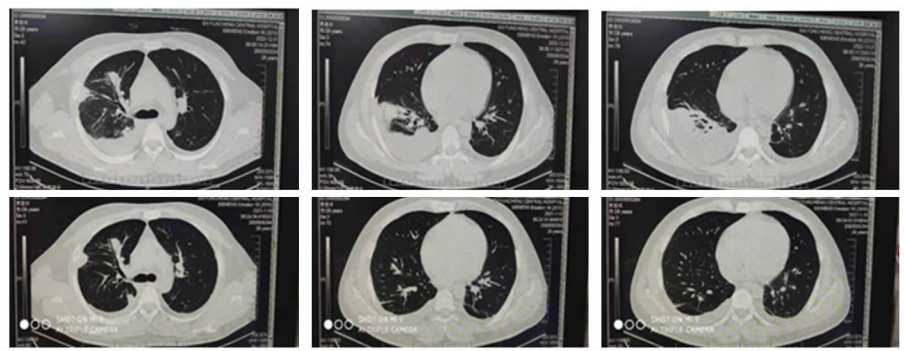


图 1 为患者急性髓系白血病 M5 化疗后肺部感染,两性霉素 B 治疗 6 天复查肺部 CT 效果明显

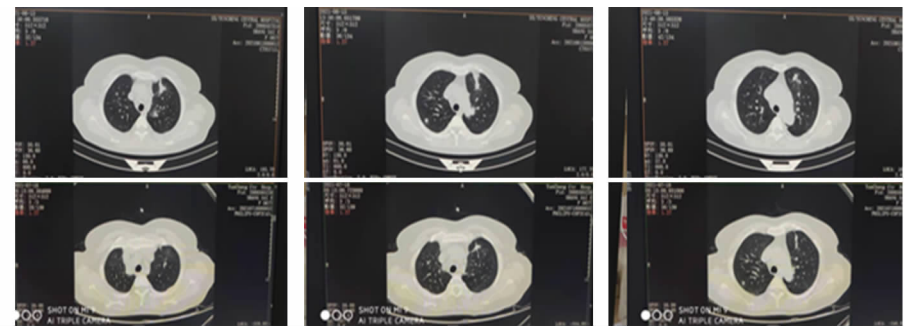


图 2 为患者急性髓系白血病 M2 化疗后出现肺部感染,两性霉素 B 治疗 22 天复查肺部 CT 效果明显

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