

促红细胞生成素(EPO)在恶性肿瘤治疗中的应用

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【摘要】 恶性肿瘤伴贫血的患者很常见,发生率为 20%~60%^[1]。化疗和放疗所致的骨髓抑制都可能造成贫血或者加重本来存在的贫血^[2]。贫血不仅能降低了患者的生存时间和生存质量(quality of life, QOL),而且还可导致肿瘤细胞低氧,降低其对放/化疗的敏感性。改善贫血是提高肿瘤患者生存时间和生存质量的关键。目前,治疗贫血的方法主要有口服补铁药物和食疗、输血以及运用促红细胞生成素(erythropoietin, EPO)。药物和食疗起效缓慢,输血也存在许多问题,因此 EPO 的使用为患者提供了另一种可选择的有效、安全的治疗方法。大量的研究证明, EPO 可明显提高患者的血红蛋白(Hb)水平、QOL 和生存率,可作为治疗贫血的常规方法。

【关键词】 促红细胞生成素;贫血;肿瘤治疗

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1 EPO 的分子结构和作用机制

促红细胞生成素(erythropoietin, EPO)是一种耐热含唾液酸的酸性糖蛋白,相对分子质量为 3kDa,由 60%的蛋白质,165 个氨基酸残基和糖组成。EPO 90%由肾脏生成,10%来自肝脏及其他组织。EPO 基因位

于第 7 号染色体长臂 11~12 区,由 4 个内含子(1562 bp)和 5 个外显子(582 bp)构成^[3]。

正常血清中 EPO 浓度呈持续低水平状态,血清中的平均浓度约为 14.9mU/ml。EPO 是体内调节前体红细胞增殖、分化以及保持外周血红细胞浓度的最主要成分。EPO 在 Multi-CSF、GM-CSF、白细胞介素-1(IL-1)

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等因子的协助下与红系干细胞(BFU-E/CFU-E)表面的受体结合,促使其增生和成熟,并促使网织细胞从骨髓中释出。肾脏疾病、骨髓损伤、铁供应不足等均可干扰该过程。此外,EPO 还是一种有效的细胞保护因子,能增加细胞低氧条件下的生存力。当患肿瘤和严重感染时,体内产生大量的 IL-1、白细胞介素-6(IL-6)、 γ -干扰素(γ -IFN)、肿瘤坏死因子(TFN)等细胞因子,影响 EPO 生成而导致贫血。

EPO 受体(Epo-R)可在造血细胞以及恶性肿瘤细胞上表达。研究证实 Epo-R 表达与肿瘤浸润有关^[4],且主要表达在低氧区肿瘤细胞坏死区域附近和肿瘤浸润的边缘^[5],阻断该受体能明显减小肿瘤的体积。动物实验表明,EPO 能增加肿瘤细胞对放疗和化疗的敏感性。小鼠肺癌模型的研究表明 EPO 和抗癌药物间有协同作用,能进一步增强其抗癌活性^[6]。

2 肿瘤相关贫血和低氧的临床意义

贫血是恶性肿瘤常见的并发症,有研究证实 70% 骨髓瘤患者、50% 的肺癌和卵巢癌患者出现了贫血^[7]。导致肿瘤患者贫血的原因很多,包括肿瘤本身、与肿瘤相关的并发症以及治疗所致的骨髓抑制和肾脏损害等。

Schapira 等测定了 31 例肿瘤患者化疗前及化疗后第 1,7,14,28 天的血清 EPO(sEPO)水平,结果显示,化疗后第 7 天血清 EPO 浓度达到峰值,随后逐渐降低,至 28d 时降至峰值的 1/4,而且明显低于未化疗组($P < 0.01$)。

大量研究证实,贫血是肿瘤细胞低氧的重要原因。急性或慢性贫血的患者,因为血红蛋白的下降导致血液运送氧的能力降低;此外,在实体瘤中,肿瘤微血管结构的严重异常以及微循环紊乱使得传递给肿瘤和基质细胞的氧明显减少甚至完全消失,均可导致肿瘤细胞低氧并诱导肿瘤细胞周期停滞、分化和凋亡潜能降低,刺激蛋白转录,促进基因组的不稳定性,增加基因变异的数目,同时还能抑制细胞表面整合素基因,促进肿瘤细胞的生长播散及复发。

最终导致患者因肿瘤细胞低氧产生了治疗的抵抗,影响疗效。此外,还有研究证实在肿瘤细胞内氧分压低于 25~30mmHg 时,肿瘤细胞对放射的敏感性也明显下降,且由细胞因子和白介素-2 诱导的淋巴因子活化的杀伤细胞活性也明显降低。要在无氧情况下,达到正常氧水平下同样的生物学效应,放射剂量是后者的 3 倍。许多抗肿瘤药物(如环磷酰胺、卡铂、阿霉素)在体内和体外发挥作用过程中也需要充分的氧供

应。低氧导致的化疗药物耐药可能有多种机制参与,可抑制细胞增殖,使药物的细胞毒性下降和组织酸中毒。光动力治疗介导的细胞死亡同样也离不开氧,低氧条件下光动力治疗疗效降低。

3 EPO 治疗肿瘤相关性贫血

目前治疗贫血的方法主要有输血、补充铁剂的药物、食疗和 EPO 治疗。输血可快速有效提升 Hb 水平并改善生存质量(QOL)2~4 周,但不方便且存在安全隐患。有研究表明肿瘤患者输血可能造成肿瘤的播散和转移。

大量的随机对照试验证明人类重组促红细胞生成素(rHuEPO)对肿瘤或放/化疗导致的贫血患者有明确的疗效和耐受性。EPO 能使 32%~82% 患者的 Hb 上升 $> 2g/dl$,明显减少了输血并改善了 QOL^[8-13]。

临床上 rHuEPO 的主要适用人群为^[14]:① Hb $< 10.5g/dl$,或 Hb $\geq 10.5g/dl$ 但有贫血症状的患者;② 内源性 EPO 水平低下($< 100 mU/ml$)者;③ 有一定干细胞储备的贫血患者;④ 化疗 1 个疗程后 Hb 明显降低($1 \sim 2g/dl$)者;⑤ 放疗,特别是头颈部肿瘤的患者。

Ludwig^[15] 等研究表明血清 EPO(sEPO)水平 $< 100IU/L$ 的患者在接受 EPO 治疗 2 周后,若 Hb 升高 $> 0.5g/dl$,则能准确判断治疗有效的阳性预测值为 95%。网织细胞 $> 40 000/\mu l$ 和较高的可溶性铁传递蛋白受体浓度($> 25\%$)也可作为判断 EPO 治疗有效的指标。研究表明影响 EPO 疗效的两个主要因素为功能型铁缺乏和血清叶酸水平低,故建议在 EPO 使用同时预防性补充铁剂和叶酸^[16]。此外,有研究证实有输血史的患者 EPO 治疗的耐受性较差。EPO 治疗的主要不良反应有:① 在注射点有疼痛感或红斑;② 高血压:特别是在接受大剂量 EPO 治疗的慢性肾脏疾病患者中,发生高血压的较多;③ 红细胞发育不全(PRCA),也在慢性肾脏疾病患者中发生,但肿瘤患者中未发现以上不良反应;④ 可能刺激肿瘤细胞的生长:特别是肿瘤细胞表面有 EPO 受体的患者。

目前,用于临床的 rHuEPO 共有 3 种,分别是:epoetin alfa, epoetin beta, darbepoetin alfa。其中只有 Epoetin alfa 和 darbepoetin alfa 被准许应用于实体肿瘤和非骨髓恶性肿瘤的化疗患者中。其平均半衰期均为 8h。常规用法为 10 000IU/次或 150IU/(kg·次),皮下注射,3 次/周,最少 4 周。疗效不佳者可增加到 300IU/(kg·次),3 次/周,再用 4~8 周^[17-19]。美国临床肿瘤协会(ASCO)和美国血液学协会(ASH)制定了 EPO 在肿瘤患者中的临床使用原则^[20]:① EPO 推荐用于化疗相关

的贫血, $Hb \leq 10g/dl$ 。红细胞(RBC)悬液输注也是一个选择,这取决于贫血的严重程度和临床情况。②患者 Hb 水平降至 $< 12g/dl$ 时可根据临床情况决定是否接受 EPO 治疗。严重贫血的患者,也可输注 RBC 悬液。③推荐剂量是根据 EPO 每周 3 次皮下给药的大量实验数据制定的。推荐的起始剂量为 $150IU/kg$, 3 次/周,至少 4 周,对起始剂量没有反应的患者,可考虑给药剂量按比例上升至 $300IU/kg$, 3 次/周,再持续 4~8 周。也可以使用每周 1 次的用法(40 000IU)。④持续的 EPO 治疗超过 6~8 周无反应(例如, Hb 上升 $< 1 \sim 2g/dl$),则说明使用本品无效。在排除铁缺乏的情况下,应停止使用。⑤ Hb 升高到 $12g/dl$ 时, EPO 的剂量可边增加边观察,直到维持到一定水平,或者在 Hb 水平降至近 $10g/dl$ 时重新开始使用。⑥铁的基线值和定期监测,总铁蛋白结合能力,转铁蛋白饱和剂量或铁蛋白水平以及起始补铁量等,对决定 EPO 的使用量以及最大程度改善患者症状和分析 EPO 治疗失败的原因有主要价值。⑦ EPO 治疗化疗导致贫血的骨髓瘤,非霍奇金氏淋巴瘤或者慢性淋巴细胞贫血患者,应该按照上述概要的推荐方法。⑧若联用化疗和皮质激素治疗的患者,治疗后 Hb 水平未升高,则 EPO 使用应该和概要的标准相一致。

综上所述,贫血可严重影响肿瘤患者的 QOL 和预后, EPO 在化疗患者中的运用不仅明显改善患者的 QOL 和预后,也大大降低了输血次数及其并发症。但在使用时应严格遵循 ASCO/ASH 的指导方针。

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