

移植前高血清铁蛋白对急性髓系白血病及骨髓增生异常综合征预后影响研究新进展

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Advances in pre-transplantation high serum ferritin on the prognosis of acute myeloid leukemia and myelodysplastic syndrome

Summary Iron overload, a pathological state, is the body's iron stores up-regulated, which could cause damages occurred in many organs through the production of reactive oxygen species. Iron deposition in various organs, which not only affects the prognosis of patients but also might influence the progression of the underlying diseases. Serum ferritin (SF) has a limited specificity in terms of assessing the extent of the iron overload (defined as SF > 1 000 ng/ml), because the SF levels can be influenced by the acute infection, inflammation and malignancies. Many researches have recently proved that the elevated SF prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) have a negative impact on the prognosis of patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). However, the clinical cut-off value of pre-transplantation elevated SF associated with the poor prognosis of AML and MDS patients undergoing allo-HSCT ranging from 500 to 2 500 ng/ml, varied considerably. We comprehensively searched the China National Knowledge Infrastructure, PubMed and Web of Science, with the purpose of systematic reviewing the latest progress of researches focused on investigating the prognostic role of pre-transplantation elevated SF in patients with MDS and AML who underwent allo-HSCT.

Key words serum ferritin; acute myeloid leukemia; myelodysplastic syndrome; clinical cut-off value; prognosis

铁过载是体内铁含量增高,通过诱导产生活性氧继而导致机体内多种脏器损伤的一种病理状态。过多的铁沉积在不同的组织器官中,不仅影响机体基础疾病的进展,而且影响患者的预后。血清铁蛋白(serum ferritin, SF)评价体内铁过载(SF > 1 000 ng/ml)程度的特异性较差,是由于急性感染、炎症及恶性肿瘤亦会影响机体 SF 水平。近年来有多篇研究证实,异基因造血干细胞移植(allogeneic hematopoietic stem cell transplantation, allo-HSCT)术前 SF 水平升高是骨髓增生异常综合征(myelodysplastic syndrome, MDS)及急性髓系白血病(acute myeloid leukemia, AML)患者移植术后的不良预后因素之一,但文献报道的关于 SF 的临床干预阈值差异大(500~2 500 ng/ml)。本文在系统检索近年来中国知网、PubMed 及 Web of Science 收录的有关研究 allo-HSCT 术前高 SF 水平与 MDS 和(或)AML 患者预后关系的文献基础之上,就当前该研究领域的进展加以综述。

1 机体的铁含量分布、吸收运输过程及铁代谢的调控机制

铁是人体的必需营养元素之一,是细胞生命活动及酶促反应的主要辅助因子^[1]。人体的总铁含量为 3~4 g,主要分布于血红蛋白(约含 2 g 铁)、巨噬细胞和肝细胞储存铁蛋白(约含 1.5 g 铁)、肌红

蛋白(约含 0.3 g 铁)、血浆中的转铁蛋白(2~4 mg 结合铁)及少量参与细胞代谢活动的含铁蛋白^[2]。血浆中大部分铁来源于脾脏巨噬细胞吞噬衰老的红细胞(约含 1 g 铁);此外还有一部分来源于肠道上皮细胞的膳食吸收,该部分铁主要用于补充每日上皮细胞脱落引起的铁丢失量(1~2 mg)^[2]。Fe²⁺由位于十二指肠细胞刷状缘膜的二价金属转运体 1(DMT1)运输入肠上皮细胞内,继而由位于肠上皮细胞基底膜、巨噬细胞和肝细胞窦表面的铁转运蛋白运送入血^[3]。生理条件下,机体内的多种调控蛋白通过调节膳食铁吸收量及巨噬细胞吞噬再利用的铁继而调节人体的铁含量水平,这种调控模式可以有效预防机体铁过载(SF > 1 000 ng/ml)的发生。然而,输血依赖性患者由于慢性输血短时间内增加了铁的摄入及吸收量,上述调节每日铁吸收量的调控模式完全失效^[4]。

肝细胞合成分泌的铁调素是机体内最重要的铁代谢调控蛋白,铁调素与位于巨噬细胞、肝细胞和十二指肠细胞上的铁调素受体——铁转运蛋白结合,继而降低铁的入血量^[5]。机体内的铁含量可以调节体内铁调素的表达水平,然而这种调节通过复杂的分子介导的调控通路实现^[6],其中主要的调控通路包括由炎症细胞因子白细胞介素 6 激活的 Janus 激酶/信号转导和转录激活因子通路(JAK-STAT3)、骨形成蛋白受体(BMPR-SMAD)信号通路^[7]。骨形成蛋白通过结合其辅助受体——铁调素调节蛋白,激活上述信号通路并增加体内的铁调

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素含量^[8]。Silvestri等^[9]研究发现,跨膜丝氨酸蛋白酶6(TMPS6)通过编码蛋白裂解酶-2(matriptase-2)抑制BMPR-SMAD信号通路继而下调铁调素的表达;此外也有研究证实在红细胞生成过程中,生长和分化因子-15(GDF15)、TWSG1及最近新发现的激素类物质Erythroferrone(ERFR)等多种活化因子可以下调铁调素的表达水平^[10-11]。机体铁含量不足及缺氧时,通过铁调节蛋白与铁反应元件相互作用产生的缺氧诱导因子刺激DMT1及转铁蛋白信使RNA的转录,继而增加巨噬细胞及十二指肠上皮细胞内的铁输出量^[12]。慢性贫血及原位溶血通过上调生长分化因子-15的表达水平而下调肝细胞合成分泌铁调素水平,继而增加十二指肠上皮细胞铁的吸收入量^[13]。综上所述,机体内铁的唯一转运体——铁转运蛋白的表达量既受铁含量的调节(在翻译水平),也受体内血红蛋白的调节(在转录水平)^[14]。

2 铁过载及其毒害反应

铁过载包括先天性铁过载和获得性铁过载。先天性铁过载见于基因突变引起的遗传性血色病;获得性铁过载主要见于对输血依赖的血液系统恶性肿瘤患者及部分肝肾疾病患者^[15]。此外,慢性贫血及原位溶血也会引起铁过载,而铁过载的程度取决于疾病本身的严重程度;慢性贫血及原位溶血会引起GDF15过度表达,继而通过抑制肝铁调素的生成促进十二指肠上皮细胞膳食铁的吸收入量^[13]。无论是先天性还是获得性的铁过载,都会沉积在不同的重要脏器中^[16]。

铁过载的毒性并不是直接来源于储存铁,而是来自于储存铁与不稳定的细胞内铁池之间的动态平衡;长期摄取非转铁蛋白结合铁、非转铁蛋白结合铁氧化还原成分及不稳定性血浆铁,会导致机体贮存铁和不稳定的细胞铁池中的含铁量增加^[16]。当不稳定的细胞内铁池的含铁量超过细胞合成新的铁蛋白分子所需铁含量的能力时,即达到了产生活性氧(ROS)的临界值^[16]。ROS增加脂质过氧化损伤及细胞器损伤,并通过介导转化生长因子1(TGF-1)通路引起细胞死亡和纤维化^[17]。此外,ROS也会损伤DNA结构,诱发基因突变、细胞死亡或肿瘤的发生^[16,18]。

3 SF

SF是铁的主要储存形式之一。SF是由去铁蛋白和铁核心 Fe^{3+} 形成的复合物,铁蛋白的铁核心 Fe^{3+} 具有强大的结合铁和贮备铁的能力,以维持体内铁的供应和血红蛋白相对稳定性。SF主要分布于肝脏、脾脏、骨髓组织中。尽管肝组织活检是评估机体铁过载程度的金标准,但是肝组织活检会发生出血、感染等不良并发症^[19]。SF检测方便、简易,广泛用作评估体内铁过载的替代指标^[20]。然而

SF评估机体铁含量的特异性备受争议,因为SF亦是一种急性反应蛋白,其水平会受到急性感染、炎症及恶性肿瘤的影响^[21]。此外,磁共振成像技术及超导量子干涉仪生物磁性肝脏磁化率计也被用于评估机体铁过载,然而文献报道这两种技术评估机体铁过载的能力不及SF^[21-22]。

4 MDS及AML患者allo-HSCT术前SF水平升高的临床预后价值

MDS是起源于造血干细胞或祖细胞的一组异质性克隆性疾病,其特征是无效造血、血细胞减少及具有高风险向AML转化的潜力^[4]。AML是一组血液系统恶性肿瘤疾病,主要表现为骨髓、血液等组织的增生、克隆、异常分化,有时甚至是造血系统低分化细胞的浸润^[23]。化疗及allo-HSCT是AML和(或)MDS患者当前的主要临床治疗策略。AML及MDS患者的预后依然不容乐观,即使接受allo-HSCT的AML和(或)MDS患者的5年总体生存率也仅为36%~54%^[19,24-26]。Allo-HSCT移植术前铁过载可引起肝功能损害、肝窦梗阻综合征、感染等并发症,继而严重影响长期生存率及增加移植相关的死亡率^[19,27]。

铁过载已经被证明是allo-HSCT后MDS和(或)AML患者的重要不良预后因素之一^[4,16]。尽管近年来很多临床研究证实了allo-HSCT术前SF水平升高与AML和(或)MDS患者移植术后的不良预后相关,但文献报道的与AML及MDS预后相关的SF的临床截断值及SF的临床预后价值并不全相同。近年来有关该研究的主要结果见表1。

尽管SF评估机体铁含量的特异性备受争议,但SF已广泛用于评估体内铁过载程度的替代指标。如表1所示:Kikuchi等(2012)及Li等(2013)研究发现,allo-HSCT术前 $\text{SF} \geq 500 \text{ ng/ml}$ 的AML和MDS患者整体生存率明显低于移植前 $\text{SF} < 500 \text{ ng/ml}$ 的患者,且多因素回归分析证实allo-HSCT术前 $\text{SF} \geq 500 \text{ ng/ml}$ 是AML及MDS患者预后的独立危险因素;5项回顾性研究^[19-20,24,28-29]发现,allo-HSCT术前 $\text{SF} \geq 1000 \text{ ng/ml}$ 的AML和MDS整体生存率明显低于移植前 $\text{SF} < 1000 \text{ ng/ml}$ 的患者,此外,多因素回归分析也证实allo-HSCT术前 $\text{SF} \geq 1000 \text{ ng/ml}$ 是AML及MDS患者预后的独立危险因素;Jang等^[30]、Lim等^[31]及Artz等^[32]分别以allo-HSCT术前 $\text{SF} \geq 1400 \text{ ng/ml}$ 、 $\text{SF} \geq 1500 \text{ ng/ml}$ 及 $\text{SF} \geq 2500 \text{ ng/ml}$ 作为SF的临床截断值,3项研究均未发现allo-HSCT术前SF与AML及MDS患者的不良预后相关。Yan等^[33]最近发表的一篇纳入所有接受allo-HSCT的血液系统恶性肿瘤患者的meta分析的亚组分析结果显示,allo-HSCT术前 $\text{SF} \geq 1000 \text{ ng/ml}$ 是血液系统恶性肿瘤患者的不良预后因素。此外,Pileggi

表 1 纳入研究的基本信息

作者	疾病类型 (例数)	患者入 组时间	研究 类型	男/女 (例)	年龄 中值 (范围) /岁	移植前 SF 含量 /(ng · ml ⁻¹)		HR(95%CI)
						截断值	中值(范围)	
Artz	AML(626)	2000—2010	前瞻性	402/382	50 (18~78)	2 500	1 148 (51~14 298)	OS:1.15(0.86~1.54) TRM:1.26(0.84~1.88)
	MDS(158)							
Tachibana	AML(118)	2000—2010	回顾性	96/57	46 (18~63)	1 000	1 139 (22~6 262)	OS:1.79(1.11~2.91)
	MDS(35)							
Tachibana	AML(99)	2000—2008	回顾性	64/55	41 (18~63)	1 000	973 (31~11 500)	OS:3.25(1.71~6.17)
	MDS(20)							
Kim	AML(32)	2000—2006	回顾性	20/18	42.5 (16~55)	1 000	1 992 (6~9 580)	RFS:3.50(1.04~12.00)
	MDS(6)							
Lim	AML(36)	2000—2006	回顾性	51/48	51 (19~72)	1 500	—	OS:2.00(0.97~3.57) TRM:1.79(0.75~4.35)
	MDS(63)							
Jang	AML(74)	2006—2012	回顾性	34/40	35 (18~72)	1 400	980 (7~11 800)	OS:1.88(0.88~4.01) RFS:1.99(0.97~4.07)
	MDS(244)							
Alessandrino	AML(113)	1997—2007	回顾性	195/162	49 (18~72)	1 000	—	OS:1.40(1.09~1.81) TRM:1.42(1.03~1.95)
	MDS(191)							
Li	MDS(191)	2005—2010	回顾性	119/72	50 (12~83)	500	—	OS:3.53(1.90~6.60)
	MDS(767)							
Komrokji	MDS(767)	2001—2009	回顾性	—	69	1 000	—	OS:1.40(1.10~1.90)
	MDS(47)							
Kikuchi	MDS(47)	1993—2001	回顾性	28/19	65 (27~74)	500	—	OS:1.90(1.03~3.50) RFS:21.16(2.06~217.10)
	MDS(47)							

OS:整体生存率;RFS:无复发生存率;TRM:移植相关的死亡率。

等^[34]在近期研究 SF 与 MDS 患者预后关系的 meta 分析中发现,allo-HSCT 术前 SF ≥ 300 ng/ml 不增加 MDS 患者的死亡风险;allo-HSCT 术前 SF ≥ 500 ng/ml 及 SF $\geq 1 000$ ng/ml 均与 MDS 患者的不良预后相关。

5 小结与展望

铁调素、DMT1、铁转运蛋白及 JAK-STAT3 等信号分子/通路参与机体内铁稳态的调控。机体铁过载时通过产生 ROS 增加脂质过氧化损伤及细胞器损伤,并通过介导 TGF- β 1 通路引起细胞死亡和纤维化;此外,ROS 也会损伤 DNA 结构,诱发基因突变、细胞死亡或肿瘤的形成。Allo-HSCT 术前铁超载可引起肝功能损害、肝窦梗阻综合征、感染等并发症,继而严重影响移植相关的死亡率和长期生存率。SF 是当前广泛使用的评估体内铁过载的非特异性替代指标,近年来小样本的临床研究证据表明 allo-HSCT 术前 SF ≥ 500 ng/ml 或 SF $\geq 1 000$ ng/ml 是 AML 和(或)MDS 患者预后的独立危险因素。

MDS 及 AML 是血液系统的异质性、恶性、克隆性疾病,MDS 及 AML 患者的预后与疾病分型、突变位点、C-反应蛋白及 SF 等多种临床病理因素相关。在精准医疗的背景下,任何与疾病预后相关的可控性危险因素都应预防性干预,allo-HSCT 术

前铁螯合剂降铁治疗已被证明有助于改善 MDS 及 AML 患者的预后。然而当前依然缺乏有关最佳的铁螯合剂治疗时间窗的研究证据,未来需要大样本、多中心的前瞻性研究来指明 SF 升高的 MDS 及 AML 患者接受 allo-HSCT 术前降铁治疗的最佳时间窗。

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