·综述·

儿童皮肤淋巴瘤的治疗进展

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【摘要】 儿童皮肤淋巴瘤是指原发于皮肤的有明显异质性的一组淋巴增殖性疾病，分类主要依据WHO-EORTC和WHO系统。最常见类型为皮肤成熟T细胞淋巴瘤与皮肤成熟B细胞淋巴瘤。儿童皮肤淋巴瘤罕见，因临床表现与成人有差异及临床试验少、用药更慎重等原因，治疗方法主要基于个案报道。治疗包括局部外用药、光疗、放化疗、手术、干细胞移植及新型药物治疗等。各类型皮肤淋巴瘤的治疗方法与疗效差异大，保守治疗在大多数儿童期蕈样肉芽肿以及其他惰性生物学特征的皮肤淋巴瘤中有效，具有侵袭性生物学特征的皮肤淋巴瘤仍需化疗、靶向治疗等。侵袭性皮肤淋巴瘤在儿童较成人比例高，需重视系统评估与随访观察。

【关键词】 淋巴瘤；皮肤；淋巴瘤，T细胞；淋巴瘤，B细胞；儿童；治疗应用

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【Abstract】 Pediatric cutaneous lymphomas are a group of lymphoproliferative diseases with obvious heterogeneity, which are primarily derived from the skin. The classification is mainly based on the WHO-EORTC and WHO systems. The most common types of primary cutaneous lymphomas in children are cutaneous mature T-cell lymphomas (CTCL) and cutaneous mature B-cell lymphomas (CBCL). Pediatric cutaneous lymphomas are rare, and their treatment approaches are mainly based on some case reports because of their clinical manifestations different from those of adults, few clinical trials and cautious medication. Treatments include topical drugs, phototherapy, radiotherapy, chemotherapy, surgery, stem cell transplantation and some new drugs. There are great differences in the therapeutic approaches and responses among various types of cutaneous lymphomas. Conservative treatment is effective in most childhood mycosis fungoides and other cutaneous lymphomas with inert biological features, while invasive cutaneous lymphomas still require chemotherapy and targeted therapies. Invasive cutaneous lymphomas occur more frequently in children than adults, so more attention should be paid to systematic assessment and follow-up observation.

【Key words】 Lymphoma; Skin; Lymphoma, T-cell; Lymphoma, B-cell; Child; Therapeutic uses

儿童皮肤淋巴瘤是原发于皮肤的有明显异质性的一组罕见淋巴增殖性疾病。因其临床表现与成人有差异以及临床试验少、用药更为慎重等原因，治疗方法主要基于个案报道。概述各类型儿童皮肤淋巴瘤的治疗现状与进展，为临床工作者提供参考。

1 皮肤T细胞淋巴瘤(CTCL)

1.1 惰性生物学特征的CTCL：

1.1.1 蕈样肉芽肿(MF)：儿童最常见的皮肤淋巴瘤，发病年龄常＜10岁。儿童MF临床表现多样，色素减退型及孤立性病变最常见[1-2]。已有的报道中，患者多数为早期(ⅠA期/ⅠB期)，仅有3例ⅡB期的报道[1]。治疗主要为局部治疗，包括光疗、局部糖皮质激素、贝扎罗汀、卡莫司汀软膏、氮芥、局部放疗及皮损切除术，可单独或联合应用[3]。近年来，光疗的作用得到重视，一线治疗包括窄谱中波紫外线(NB-UVB)和光化学疗法(PUVA)。一项单用NB-UVB或PUVA治疗儿童ⅠA/ⅠB期MF的研究中，完全或部分缓解为86%，且PUVA缓解期更长。PUVA联合甲氨蝶呤、贝扎罗汀或干扰素α-2b治疗早期MF也有良好的疗效，但联合治疗是否优于单一疗法尚不确定。由于口服补骨脂不良反应较大，NB-UVB更适用于儿童MF，特别是斑片期患者的治

疗[4]。色素减退型MF的治疗包括单用局部糖皮质激素或与NB-UVB、PUVA联合[5]。一项儿童色素减退型MF回顾性研究显示,45.7%的患者经光疗后症状显著改善,但治疗停止后20%的患者复发,仅有7%患者完全缓解,1例在5年后进展至肿瘤期[6]。对于孤立性病变,光动力可作为常规治疗无效患者的替代治疗方案[7]。对于难治性及晚期MF,有经局部电子束照射肿瘤,后全身PUVA照射与干扰素α联合治疗儿童ⅡB期MF达到完全缓解的报道[8]。已有儿童晚期MF患者应用同种异体干细胞移植进行治疗的报道,同种异体干细胞移植可诱导患者持续完全缓解,但感染、复发、死亡率较高[9]。

1.1.2 原发性皮肤CD30⁺淋巴增殖性疾病:

淋巴瘤样丘疹病(LyP):较成人少见,可出现3种不同发病模式:①初次疾病爆发后,发病频率及每次发作时的皮损数目逐渐减少,直至痊愈;②病变在广泛分布前,可数年局限于同一部位;③可出现数百个皮损[10]。本病有复发性、自愈性,治疗反应存在较大的异质性,且儿童与成人临床表现差异大,确定治疗是否有效十分困难,尚无定论。皮肤靶向治疗主要用于缓解症状,口服药物系统治疗用于症状严重且病变较多者。Wieser等[11]总结139例儿童LyP患者,其中58例接受单一方法治疗,50例分别接受2~5种不同方法的联合治疗,31例未接受治疗。治疗主要是外用或口服糖皮质激素、口服抗生素、PUVA、UVB、甲氨蝶呤、类视黄醇、他克莫司、抗组胺药、甘草酸二钠、多塞平、槲寄生提取物等治疗,各方法疗效的个体差异大。建议当皮损剧烈瘙痒或多发溃疡等时才应积极治疗。LyP易继发其他淋巴瘤,特别是MF、霍奇金淋巴瘤、间变性大细胞淋巴瘤。现有治疗不能预防继发性淋巴瘤的发生,虽然儿童发生的可能性较成人小,但Nijsten等[12]报道的35例儿童患者中有3例发生非霍奇金淋巴瘤,1例患有LyP的13岁女性患儿继发系统性间变大T细胞淋巴瘤,接受化疗及同种异体骨髓移植治疗,6年后LyP复发[13]。LyP患儿应终身随访,以尽早识别可能出现的相关恶性淋巴瘤。

原发性皮肤间变性大细胞淋巴瘤(C-ALCL):C-ALCL占儿童原发性皮肤T细胞淋巴瘤的1/3,临床病理特征及预后与成人类似[14]。通常表现为单发或局限性丘疹、结节或肿块,部分患者可表达ALK。儿童C-ALCL不论接受何种治疗方式,均预后良好,两年存活率可达100%[15]。多数患者仅接受手术切除或局部放疗,累及系统时才推荐使用化疗。Pulitzer等[14]认为,即使表达ALK,儿童也不需要像成人患者一样积极治疗。SGN-30是针对CD30抗原的新型靶向抗体-药物耦联物,已在Ⅱ期临床试验中取得较满意的疗效,总反应率73%,完全缓解率35%[16]。Mikles等[17]报道1例经化疗及同种异体造血干细胞移植后2次复发的ALCL儿童患者,使用SGN-30单药治疗,持续缓解数月。SGN-30为复发性难治性或有多系统累及的儿童患者提供靶向治疗的可能性。

1.1.3 皮下脂膜炎样T细胞淋巴瘤(SPTL):预后优于成人,治疗反应率差异大,尚无标准治疗方案。对于惰性表现的患者,随访观察,口服激素可作为一线治疗,避免过早系统治疗,甚至有研究提出儿童SPTL患者仅在发生噬血综合征时有治疗的必要[18]。BFM-NHL-90化疗方案[诱导缓解I(长春新碱,柔红霉素,左旋门冬酰胺酶,泼尼松)+CAM(环磷酰胺、阿糖胞苷、6巯基嘌呤),巩固方案M(6巯基嘌呤、甲氨蝶呤)]结合自体干细胞移植,可有效治疗发生噬血综合征的难治性SPTL[19]。

系统治疗一般采用联合化疗方案。贝扎罗汀在儿童及成人Ⅳ期患者中反应率均较高,可作为晚期SPTL的治疗选择。Huppmann等[20]应用多种方案治疗9例儿童SPTL,56%的患者复发,治疗方案分别是IS方案(泼尼松、他克莫司、环孢素)、CHOP及单用环孢素,接受多药(左旋门冬酰胺酶、甲氨蝶呤、阿霉素、长春新碱、卡莫司汀、泼尼松)联合治疗的1例未复发,CHOP方案后使用贝扎罗汀维持治疗的1例未复发,除1例因意外过量用药出现并发症死亡外,其余均长期存活。

1.2 具有侵袭性生物学特征的CTCL:

1.2.1 结外NK/T细胞淋巴瘤,鼻型(ENTNT):与成人患者相比,儿童皮肤侵袭性淋巴瘤的比例高。一般采取多药化疗,但疗效不满意,预后差。Maciejka-Kemblowska等[21]对4例儿童Ⅱ或Ⅲ期ENTNT患者,使用不同化疗方案,仅1例接受2个周期SMILE方案(甲氨蝶呤+环磷酰胺+左旋门冬酰胺酶+依托泊苷)的患者存活。Michot等[22]对13例局限性ENTNT患者(包括儿童及成人),诱导阶段予2周期ESHAP(依托泊苷、糖皮质激素、高剂量Ara-C及铂)联合40 Gy剂量放疗,巩固阶段予单独2周期ESHAP化疗,治疗有效率明显优于其他化疗方案,92%患者达完全缓解,2年生存率72%,但巩固阶段有62%患者发生血液学不良事件,其中92%为3~4级血液学不良事件。

1.2.2 种痘水疱病样淋巴增殖性疾病：本病与EB病毒感染有明确相关。多发生在中南美洲及亚洲儿童，成人罕见。尚无治疗标准，治疗包括化疗、放疗及免疫治疗等，易复发，预后差，需重视系统评估与随访[23]。Barrionuevo等[24]报道以CHOP为基础的化疗完全缓解率最高，但不良反应严重。一项研究中4例患儿接受干扰素肌内注射，皮损均有好转，但总体预后不详[25]。在两项分别纳入12例及20例患者的研究中，患者均接受放疗联合免疫抑制治疗，但大多数患者死亡[26-27]。新型药物如叶酸类似物、组蛋白脱乙酰酶抑制剂、蛋白酶抑制剂、核苷类似物等是否有效尚待进一步研究。

1.2.3 原发性皮肤侵袭性亲表皮$CD8^+$细胞毒性T细胞淋巴瘤（$CD8^+$ AECTCL）：该病临床进展迅速，即使早期放化疗，预后仍较差。Kato等[28]在儿童$CD8^+$ AECTCL患者中发现，TP53基因组不稳定性，特别是染色体不稳定性和单倍体不足，后者可能引起p14ARF-Mdm2-p53抑制蛋白途径的改变，使得肿瘤抵抗放化疗，造成快速生长与多处转移。

2 皮肤B细胞淋巴瘤（PCBCL）

因PCBCL疾病多为惰性，治疗不应过于积极，除糖皮质激素、氮芥、贝扎罗汀等局部治疗外，还可用手术切除、放疗、化疗、干扰素α、单克隆抗体。疾病呈侵袭性表现时多采取化疗。

2.1 原发皮肤边缘区B细胞淋巴瘤（PCMZL）：与成人相似，生物学惰性，预后佳。对于局部病灶或多发小病灶患者，可观察随访、手术或局部放疗，频繁复发者可局部使用糖皮质激素[29]。Amitay-Laish等[30]回顾了11例年龄＜20岁的PCMZL患者，治疗包括病灶内糖皮质激素、手术切除等非放疗方法，部分患者仅观察随访，随访5年均未出现系统累及。Servitje等[31]的研究显示，放疗和手术是最常见的治疗方法，疗效无显著差异，但手术切除更易出现原发病灶部位的复发。部分研究中无论病灶内还是静脉注射利妥昔单抗都仅使多数患者部分缓解，而另一些研究中病灶内注射该药可使74% PCMZL患者完全缓解[31-32]。Väkevä等[33]认为，疗效及复发率主要与疾病本身相关。Kempf等[34]报道的PCMZL患儿体内未检测到螺旋体，但对抗生素治疗有反应，表明或许有疏螺旋体属之外的病原体参与本病的发病。

2.2 原发皮肤滤泡中心B细胞淋巴瘤（PCFCL）：儿童患者报道少，尚不清楚其治疗方法及预后是否与成人相同。Condarco等[35]报道了外科手术成功治疗儿童PCFCL的个案。Ceppi等[29]建议对儿童PCFCL采取外科切除，复发患者予以延迟放疗。

3 结语

儿童皮肤淋巴瘤的治疗仍具有挑战性。大多数皮肤惰性淋巴瘤经保守治疗可获得满意疗效，有侵袭性的皮肤T细胞淋巴瘤需采取积极治疗如化疗、靶向治疗等。因这些疾病在儿童罕见，大规模随机临床试验可行性低，因此，有必要开展多中心儿童皮肤淋巴瘤临床大数据管理，以选择最佳治疗方式。复杂儿童皮肤淋巴瘤的诊治应由皮肤科、儿童血液病理科及血液科医师共同完成。

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