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·综 述·

乳腺癌骨转移患者预后相关因素

Prognosis related factors in breast cancer patients with bone metastasis

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[摘 要] 乳腺癌是世界范围内女性最常见的恶性肿瘤,高达75%的患者最终会发生骨转移。骨转移发生风险与肿瘤分子分型、组织病理和患者生理阶段等密切相关,骨转移合并其他部位转移、发生骨相关事件、骨转移灶的特点等都可影响患者的预后。目前临床广泛应用的骨转移治疗方法包括全身应用抗肿瘤药物和骨改良药物、局部行骨转移灶放疗和骨转移灶手术。除抗肿瘤药物外的其他治疗手段都有望改善患者预后。近年来发展的骨转移治疗新手段,如对乳腺癌原发灶的处理、放射性物质镭、骨转移关键信号分子抑制剂和某些新技术应用在提高患者生存方面都有良好的前景。本文就乳腺癌骨转移患者的预后相关因素作简要综述。

[关键词] 乳腺癌,骨转移,预后
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乳腺癌是女性中发病率最高的恶性肿瘤,虽然病死率呈下降趋势,但仍是恶性肿瘤中第二大死亡原因[1-2]。骨是乳腺癌患者最常见的远处转移部位[3]。在初诊乳腺癌时,5%~6%的女性已经发生骨转移;在乳腺癌进展过程中,约有50%患者以骨为首发转移部位[4];65%~75%的患者最终发生骨转移[5]。虽然骨转移与其他部位转移相比,患者预后相对较好[6],但近40%的患者在发生骨转移后1年内就出现骨痛、病理性骨折等骨相关事件(skeletal-related events,SREs)[7],不仅严重影响患者生活质量,而且对患者预后产生不良影响。在发生骨转移的患者中,不同的临床特征会影响患者的治疗决策及预后。因此,研究骨转移性乳腺癌(bone metastasis breast cancer,BMBC)患者的预后相关因素对于患者的治疗方案和时机选择具有重要意义。

1 乳腺癌骨转移人群特征

研究表明,骨转移的发生风险与乳腺癌原发灶的分子分型、组织病理学和患者的年龄及绝经状态密切相关。

1.1 分子分型

除基底型乳腺癌外,骨是所有乳腺癌亚型中最常见的转移部位[8-10],且更常见于Luminal A亚型[11-12]和Luminal B亚型[13],这与雌激素受体(estrogen receptor,ER)阳性是骨转移的危险因素的研究结论一致[14-15],ER阳性患者术后发生骨转移的风险可达ER阴性患者的5.2倍[16]。人类表皮生长因子受体-2(human epidermal growth factor receptor-2,HER-2)过表达与ER在介导骨转移的机制上可能存在某种协同作用,ER阳性且HER-2过表达患者较单纯ER阳性或Her-2过表达患者的骨转移发生率更高[17-18],但其中具体机制仍有待研究阐明。

1.2 组织病理学

肿瘤原发病灶直径>2 cm即肿瘤负荷大、组织学分级高、浸润性癌、淋巴结受累以及分期较晚是发生骨转移的独立危险因素[5, 14-15, 19-20]。淋巴结受累患者术后发生骨转移的风险可达淋巴结阴性患者的5.2倍[16];具有≥4个腋窝淋巴结转移和首次复发部位为局部/区域或远处软组织的患者,骨转移发生率最高[5, 21-22]。此外,双侧乳腺癌(bilateral breast cancer,BiBC)患者发生骨转移概率明显高于单侧乳腺癌(unilateral breast cancer,UBC),很可能与BiBC淋巴结分期更晚相关[23]。

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1.3　患者年龄和绝经状态

研究[5, 14-15]证明，年龄≤40岁的女性更易发生骨转移，而年龄较大或可理解为低雌激素水平对骨转移具有一定的保护作用。但在三阴性乳腺癌（triple-negative breast cancer，TNBC）中，年龄>49岁的绝经后患者也被证明为骨转移易患因素[19-21]。这提示若患者体内雌激素水平较高，且肿瘤细胞表达ER，肿瘤细胞迁徙到骨的速度较快；而在TNBC亚型患者中，激素水平对肿瘤增殖不发挥作用，但绝经后女性骨骼微环境失去了雌激素保护作用，使骨容易成为肿瘤细胞的转移部位。但其中的复杂机制需要更多的基础研究去探索和发现。

2　乳腺癌骨转移患者预后相关因素

2.1　合并内脏转移

是否存在内脏转移是影响骨转移患者预后的重要因素，合并内脏转移的骨转移患者生存率明显下降[5, 14, 24]。这提示发生内脏转移的患者已处于肿瘤发展的晚期阶段，肿瘤负荷大、耐药肿瘤细胞数量多，因而对这部分患者的治疗要采取更加积极的措施才能更好地控制病情发展。

2.2　合并SREs

研究[4, 25-26]证明，无论乳腺癌治疗方案或疾病的确诊阶段如何，与无骨转移的患者相比，发生SREs的患者预后更差，死亡风险显著增加。因此，延缓和治疗SREs对改善乳腺癌患者预后有重要意义。而SREs最常见于溶骨性骨转移，间接提示了骨转移类型对患者预后的影响可能有所不同，溶骨性较成骨性和混合性骨转移具有更大的破坏性，所以对该类型病灶的治疗手段是否需要强化值得探索。

2.3　骨转移部位和数目

脊柱是乳腺癌骨转移的最常见部位[27]。因为椎体转移的并发症如脊髓压迫对患者影响更大，与其他部位相比，椎体转移的患者预后更差，5年生存率可降低25%[28]。其他转移部位如肋骨、骨盆、肩胛骨、颅骨、肱骨和肢端骨等预后相对较好，可能是因为这些部位骨的承重负荷较小和（或）对周围正常组织的压迫和侵犯对患者的运动功能影响相对较小。多发骨转移较单发骨转移预后更差，这可能与多发骨转移发生SREs概率更高有关[29]。

2.4　其　他

患者年龄越大，肿瘤分期越晚的BMBC患者预后相对更差。研究[15]发现，年龄>40岁、高肿瘤负荷、原发病灶分期晚的骨转移患者死亡风险更高。淋巴结转移数<10个、术后无病生存期（disease-free survival，DFS）>3年是激素受体阳性乳腺癌单纯骨转移的预后良好因素[30]。炎性乳腺癌（inflammatory breast cancer，IBC）患者的无进展生存期（progression-free survival，PFS）和中位总生存期（overall survival，OS）明显低于非IBC，特别是在ER阳性亚组中，这种差异更显著[31]。这提示是否应该考虑在ER阳性骨转移的IBC患者中进行内分泌治疗以外的积极干预，而最佳治疗方案的实施尚需大型、高质量的多中心随机对照临床试验去探索和证明。

3　改善预后的治疗手段

乳腺癌骨转移的治疗是以多学科参与的综合治疗，化疗、内分泌治疗和分子靶向治疗是发挥全身抗肿瘤作用的重要手段，对BMBC患者的预后起着关键作用。骨改良药物、骨转移灶局部治疗方式的发展与发生骨转移后对乳腺原发病灶的手术与否及其时机在改善患者远期预后方面具有潜在应用价值。新治疗方法如放射性元素、骨转移关键信号分子抑制剂和先进技术平台的应用也为提高患者生存带来更多希望。

3.1　骨改良药物的应用

骨改良药物是预防和延缓SREs的标准治疗。近年来随着对该类药物研究的深入，发现其还具有抗肿瘤作用，对于改善乳腺癌患者的预后有重要意义。

3.1.1　双膦酸盐　目前以唑来膦酸（zoledronate acid，ZOL）为代表的第三代双膦酸盐在临床应用较为广泛。研究[32-34]发现，ZOL与化疗药物具有协同抗肿瘤作用，能够清除骨髓播散肿瘤细胞（disseminated tumor cell，DTC）[35-36]，可显著降低绝经（自然绝经或药物诱导绝经）后、早期乳腺癌女性骨复发风险和死亡风险[37-39]。欧洲专家组共识指南[40]建议对于低雌激素水平、有中高度复发风险的早期乳腺癌患者，可早期应用双膦酸盐以预防肿瘤转移。AZURE研究证明，对Ⅱ/Ⅲ期乳腺癌，在标准治疗的同时应用ZOL 5年，可显著改善绝经后妇女的DFS（HR=0.82）、无侵袭性疾病生存期（invasive disease-free survival，IDFS）（HR=0.78）和无骨复发生存期（bone metastasis-free survival，BMFS）（HR=0.76）；且v-maf鸟类肌筋膜纤维肉瘤癌基因同源物（musculoaponeurotic fibrosarcoma，MAF）基因无扩增的患者，无论其绝经状态如何，OS也有获益（HR=0.69）[41]。在绝经后女性骨微环境中，肿瘤生长受破骨细胞介导的机制驱动[42]，这可能有助于解释为何绝经后女性能从双膦酸盐治疗中获益。而未绝经患者的高雌激素水平促进ER阳性肿瘤进展的作用可能掩盖了双磷酸盐的抗肿瘤活性。这提示未来有关双膦酸盐的研究设计中，早期乳腺癌和（或）绝经后女性可能更适合作为入组条

件之一。若双膦酸盐成为改善预后的标准治疗手段，其推荐剂量和疗程、病情进展后如何更换药物或用药方法尚需不断探索改进。

3.1.2 地诺单抗 地诺单抗（denosumab）是特异性靶向核因子-κB受体活化因子配体（receptor activator of NF-κB ligand，RANKL）的单克隆抗体，阻止RANKL和其受体结合，抑制破骨细胞活性，从而减少骨质破坏和吸收，增加骨密度[43]。Denosumab与双膦酸盐相比更能降低SREs风险[39, 44]。RANKL/RANK/OPG通路参与乳腺癌的发生发展和转移[45]，原发病灶高表达RANK与患者骨转移高风险，较短BMFS和不良预后相关[46-47]，但目前的研究数据尚不支持denosumab能改善乳腺癌患者的预后。虽有研究[48]发现，循环肿瘤细胞（circulating tumor cell，CTC）阳性的BMBC患者应用denosumab治疗后，外周血CTC数目减少，这提示denosumab可能有助于抑制肿瘤细胞扩散。但荟萃分析[39]证明denosumab并不能改善骨转移患者存活率。最近的D-CARE研究[49]将denosumab用于接受新辅助或辅助治疗的高复发风险早期乳腺癌患者，证明denosumab可延缓骨转移的发生，但BMFS和DFS无获益。ABCSG-18研究[50]中，对激素受体阳性的绝经后乳腺癌患者在内分泌治疗同时应用denosumab，目前随访数据表明这种联合治疗可改善患者DFS，期待后续进展。

3.2 骨转移灶的放疗

放疗不仅能控制乳腺癌骨转移病灶的发展，还能有效预防和延缓SREs的发生。虽然目前尚无研究证明骨转移灶放疗是否可改善患者预后，但考虑到局部照射可诱导肿瘤细胞免疫原性死亡（immunogenic cell death, ICD），促进全身炎症和免疫[51]，延缓和减少了影响患者生存的SREs，放疗可能有益于提高患者生存时间，且放疗联合免疫治疗的方案可能进一步改善患者预后，值得开展进一步研究。不同放疗方式对病灶的控制率存在一定差异，研究[52]证明，虽然单次照射和分次照射在骨痛控制和副作用方面无差异，但仅接受单次照射的患者，其骨复发率更高。立体定向放射治疗(stereotactic body radiation therapy，SBRT)作为一种更加精准的放疗方式，对骨转移病灶局部控制率更高，降低骨复发风险，症状缓解期也相对延长[53-56]。但现有的SBRT治疗骨转移的循证医学证据多来自于回顾性临床研究及I/II期临床试验，临床上治疗对象主要集中在椎体转移及首程放疗后复发而需要再次放疗的患者，较少应用于一线治疗，因此尚缺少SBRT与患者预后相关数据。期待相关研究来证明骨转移灶放疗及其方式与患者预后之间的关联。

3.3 对骨转移灶的手术

回顾性研究[57]证明，单发骨转移灶接受完整切除较瘤内处理可提高患者生存率，对于股骨近端转移瘤，在广泛的病灶切除后予内置假体置换术的治疗效果好，模块化假体置换术后的平均存活时间为860 d，病灶复发及感染减少、肢体功能恢复良好，而单纯骨固定术后的平均生存期仅为360 d，所以单发骨转移灶完整切除联合模块化假体置换术对预后良好患者来说是更优的选择[58]。对于椎体转移导致脊髓压迫的患者，椎体重建术和介入手术是重要的姑息对症治疗手段。回顾性研究[59]证明，针对这部分患者，手术联合放疗对比单纯放疗，两组间的1年局部控制率和总生存率的差异均无统计学意义。但必须考虑到连接邻近椎体的金属支撑物（如钛合金、钽金属棒等内固定）的材质差异，可能因为影响术后放疗的剂量分布而降低放疗疗效。因此，椎体转移作为骨转移的特殊部位，患者预后相对较差，局部治疗措施的不同对患者预后的改善可能无明显差异，是否需手术与放疗联合应用需综合考虑患者的疾病状态和治疗目标等因素，为患者制定最佳治疗方案。除椎体以外的骨转移，放疗联合手术理论上仍有望改善患者预后。

3.4 对乳腺原发灶的手术

对于BMBC患者，乳腺原发病灶是否手术是临床悬而未决的问题。最近研究[15]证明，乳腺癌病灶手术对骨转移患者的预后可能起到积极作用，但仅适用于未行全身抗肿瘤治疗的患者。基于SEER数据库的分析发现，对于初诊BMBC患者，接受原发灶局部手术组的中位生存期是未手术组的1.72倍。MF07-01研究[60]旨在评估IV期乳腺癌患者先接受局部手术再联合全身治疗对比仅接受全身治疗对局部复发和患者OS的差异，中位随访时间（40个月）的结果证明，手术联合全身治疗组患者OS更高(46 *vs* 37个月，HR=0.66，*P*=0.005)，激素受体阳性、HER-2阴性、年龄<55岁以及单纯骨转移患者，原发灶手术联合全身治疗组OS更佳，两组局部进展率分别为1%和11%（*P*=0.001）。然而TBCRC 013研究[61]证明，全身治疗有效的Ⅳ期患者接受原发灶手术，其3年整体OS无改善，但未做骨转移人群的亚组分析。另一项前瞻性研究[62]证明，对一线治疗有效的IV期患者再接受原发灶的局部手术，骨转移亚组2年OS并无获益，但该研究未纳入抗HER-2治疗的患者。各研究存在患者特征和治疗方案等的选择偏移，但提示了手术时机的重要性。研究[63-66]表明，IV乳腺癌患者接受手术与预后改善有关，外科处理原发灶以降低肿瘤负荷和减少耐药细胞，再辅以术后全身治疗能够提高患者生存时间。而对于已接受全身治疗且敏感的患者再行

原发病灶的切除将难以对预后产生积极作用。另外，乳腺原发病灶手术的受益患者分层在BMBC中尚不明确，尚需更多、高质量、多中心的大型临床研究去探索。

3.5　其他可能改善乳腺癌骨转移预后的新疗法

3.5.1　二氯化镭-223　近年来，放射性物质二氯化镭-223在前列腺癌骨转移患者中的应用逐渐增多，对患者的生活质量和生存均有改善[67-69]，标志着骨转移治疗模式的转变。临床前研究[70]表明，二氯化镭-223与骨基质结合，能够抑制骨溶解，诱导肿瘤细胞DNA断裂，抑制肿瘤生长，有预防和抑制骨转移的作用。早在2014年就有病例报道[71]将FDA批准的前列腺癌治疗剂量用于1例难治性BMBC患者，患者骨痛症状消失，肿瘤和骨转换标志物水平显着下降，但PET/CT影像学评估病灶并未缩小。因此二氯化镭-223与其他放射增敏疗法如化疗或靶向疗法联合，可能产生更好的疗效。Ib期临床研究[72]表明，将二氯化镭-223与紫杉醇联合治疗包括乳腺癌在内的多个瘤种所致的骨转移，患者耐受性良好，该联合治疗方案对BMBC患者预后的影响值得进一步探索。

3.5.2　骨转移关键信号分子抑制剂　一些关键信号转导分子与骨转移的发生发展密切相关，相应的信号分子抑制剂可能对治疗骨转移和改善患者预后有重要价值。Src抑制剂如达沙替尼具有抑制破骨细胞、抗肿瘤和抗转移能力[73]，与化疗联合治疗骨转移的临床获益率可达46%[74-75]，与内分泌治疗联合可将转移性乳腺癌患者的PFS提高1倍[76]；Src活化参与曲妥珠单抗耐药[77-78]，Src抑制剂联合靶向治疗有可能克服曲妥珠单抗耐药问题。研究[79]发现，酪氨酸激酶受体c-Met蛋白参与溶骨性骨转移，小分子c-Met抑制剂和靶向编码c-Met的MET基因的特异性短发夹RNA显著抑制骨中乳腺癌细胞增殖和骨溶解[80]。c-Met配体为肝细胞生长因子（HGF），靶向c-Met/HGF通路是治疗乳腺癌骨转移的新方向[81]。此外，新型口服小分子RANKL抑制剂AS2676293[82]、缺氧诱导因子（HIF）抑制剂和骨形态发生蛋白（Bone morphogenetic protein，BMP）抑制剂[83-85]都能够抑制乳腺癌骨转移过程和骨质破坏，对治疗甚至预防骨转移有良好的应用前景，期待相关药物的研发和临床试验。未来，探索骨转移关键信号分子抑制剂与化疗、内分泌治疗和分子靶向治疗的最佳联合或序贯方案及剂量选择是乳腺癌骨转移治疗的新方向，有望提高患者预后。

3.5.3　其他先进技术的应用　有研究者[86]开发了骨靶向药物递送系统Au@MSNs-ZOL，即骨靶向纳米技术联合ZOL，不仅具有骨靶向性，而且可以抑制破骨细胞的形成并促进成骨细胞的分化，通过将Au@MSNs-ZOL与近红外照射光热疗法相结合，可以诱导癌细胞凋亡，改善骨微环境，从而抑制肿瘤的生长并延缓骨转移和骨痛发生。这一纳米平台为可辅助更高效地治疗骨转移，期待其早日应用于临床并提高患者的生存。

4　总　结

乳腺癌骨转移发病率高，不同程度地影响患者的生活质量和临床结局。确定骨转移的危险因素，有助于早期识别易发生骨转移人群，为患者制定合适的复查时间并及时给予干预手段。骨转移患者的预后与是否合并其他部位转移、是否发生SREs、骨转移灶的特点、患者生理状态以及肿瘤的生长情况密切相关。BMBC患者的全身和局部治疗手段对患者预后有着不同的影响，骨保护治疗因具有抗肿瘤作用，或许也可以归为全身治疗的一部分。对各治疗手段的受益患者分层可更精准地指导临床决策，一些新靶点的药物研发和先进技术的应用也可能对骨转移患者的预后产生积极作用。多种治疗手段的序贯或联合应用对骨转移患者预后的影响还需要更多研究去证明。

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