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肿瘤相关巨噬细胞CD68蛋白与乳腺癌临床病理特征 对新辅助化疗疗效和预后的影响

陈馨, 张薇, 张伟杰, 赵怡欣, 吴鸿雁, 姚永忠

(南京大学医学院附属鼓楼医院普外科, 南京 210008)

[摘要] 目的: 分析肿瘤相关巨噬细胞CD68蛋白与乳腺癌临床病理特征对新辅助化疗(neoadjuvant chemotherapy, NCT)疗效和预后的影响。方法: 选取2013年1月至2017年1月于南京大学医学院附属鼓楼医院收治的局部晚期乳腺癌患者172例为研究对象, 免疫组织化学检测癌组织中ER, HGR2, Ki-67以及CD68的表达, 所有患者NCT后1个月内进行手术, 分析临床病理学参数和病理完全缓解率(pathologic complete response, pCR)之间的关系。结果: CD68表达和ER呈负相关($r=-0.129$, $P=0.018$), CD68表达和HER2($r=0.211$, $P=0.011$)、Ki-67($r=0.195$, $P=0.013$)以及肿瘤直径($r=0.315$, $P=0.007$)呈明显正相关, 而CD68和患者的年龄、绝经状况以及淋巴结是否出现转移无明显关系($P>0.05$); ER阴性组pCR率(25.95%)明显高于阳性组(7.81%), 差异具有统计学意义($P<0.05$); Ki-67高表达组pCR率(32.39%)明显高于低表达组(9.90%), 差异具有统计学意义($P<0.05$); CD68高表达组pCR率(24.11%)明显高于低表达组(10.00%), 差异具有统计学意义($P<0.05$); 经过化疗后, 有131例患者(72.16%)CD68表达下降, 下降组pCR率为24.43%(32/131), 未下降组(无变化或者出现上升)患者的pCR率为2.44%(1/41), 提示化疗后CD68变化与化疗疗效相关, 差异具有统计学意义($P<0.05$); 各分子亚型和绝经状况、化疗前肿瘤直径、疗效以及化疗前CD68表达明显相关($P<0.05$), 而与年龄、淋巴结转移不相关($P>0.05$); 化疗前, CD68低表达组总生存时间(overall survival, OS)和无病生存时间(disease-free survival, DFS)均优于CD68高表达组, 差异具有统计学意义($P<0.05$)。化疗后CD68下降组OS和DFS均较未下降组延长, 差异具有统计学意义($P<0.05$)。COX多因素回归分析结果显示化疗前Ki-67、CD68、化疗后CD68变化是影响DFS的独立危险因素。结论: CD68高表达者对化疗更为敏感, 但预后差, 化疗前Ki-67、CD68、化疗后CD68变化是影响DFS的独立危险因素, Ki-67, ER, HGR2以及CD68分子亚型可以作为NCT疗效的预测指标。

[关键词] 乳腺癌; 新辅助化疗; CD68; 分子亚型

Effects of tumor-associated macrophage CD68 protein and clinicopathologic features of breast cancer on efficacy and prognosis of neoadjuvant chemotherapy

CHEN Xin, ZHANG Wei, ZHANG Weijie, ZHAO Yixin, WU Hongyan, YAO Yongzhong

(Department of General Surgery, Affiliated Drum Tower Hospital of Medical College, Nanjing University, Nanjing 210008, China)

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通信作者 (Corresponding author): 姚永忠, Email: loyal1006@hotmail.com

Abstract **Objective:** to analyze the effect of CD68 protein of tumor-associated macrophage and the clinicopathological features of breast cancer on the efficacy and prognosis of neoadjuvant chemotherapy (NCT). **Methods:** In January 2013 to January 2017, 172 cases of patients with Locally advanced breast cancer in the Affiliated Drum Tower Hospital of Medical College of Nanjing University were selected as the research objects. ER, HGR2, Ki-67, and the expression of CD68 were detected by immunohistochemical. All patients were given surgery within 1 month after NCT. Clinical pathology analysis parameters and pathological complete response rate (pathologic complete response, pCR) relationship was analysed. **Results:** CD68 expression was negatively correlated with ER ($r=-0.129, P=0.018$), CD68 expression was positively correlated with HER2 ($r=0.211, P=0.011$), Ki-67 ($r=0.195, P=0.013$) and tumor diameter ($r=0.315, P=0.007$), while there was no significant correlation between CD68 and patient age, menopausal status and lymph node metastasis ($P>0.05$). The pCR rate of ER negative group (25.95%) was significantly higher than that of the positive group (7.81%) ($P<0.05$). The pCR rate (32.39%) of the Ki-67 group with high expression was significantly higher than that of the group with low expression (9.90%) ($P<0.05$). The pCR rate (24.11%) of the group with high CD68 expression was significantly higher than that of the group with low expression (10.00%) ($P<0.05$). After chemotherapy, the expression of CD68 decreased, the pCR rate was 24.43% (32/131) in the decreasing group, and the pCR rate was 2.44% (1/41) in the non-decreasing group (no change or rise), suggesting that the change of CD68 after chemotherapy was correlated with the efficacy of chemotherapy ($P<0.05$). The molecular subtypes were significantly correlated with menopausal status, tumor diameter before chemotherapy, efficacy and CD68 expression before chemotherapy ($P<0.05$), but not with age or lymph node metastasis ($P>0.05$). Before chemotherapy, both OS and DFS in the group with low CD68 expression were superior to the group with low and high CD68 expression ($P<0.05$). After chemotherapy, both OS and DFS in the CD68 decreased group were longer than those in the decreasing group ($P<0.05$). COX multivariate regression analysis showed that the changes of ki-67, CD68 before chemotherapy and CD68 after chemotherapy were independent risk factors affecting DFS. **Conclusion:** High expression of CD68 was more sensitive to chemotherapy, but the prognosis was poor. Changes of ki-67, CD68 and CD68 after chemotherapy are independent risk factors affecting DFS, and ki-67, ER, HGR2, CD68 and molecular subtypes can be used as predictors of the efficacy of NCT.

Keywords breast cancer; neoadjuvant chemotherapy; CD68; molecular subtypes

乳腺癌作为女性临床常见恶性肿瘤,在大城市中居女性恶性肿瘤首位,发病率在(50~60)/10万,且与年龄成正比^[1],肿瘤出现转移是引起乳腺癌患者死亡的主要原因^[2]。肿瘤微环境在肿瘤转移过程中起重要作用,免疫细胞是肿瘤微环境重要组成部分,肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)作为免疫细胞代表,与肿瘤细胞相互作用,从而促进肿瘤的侵袭和转移^[3]。随着乳腺癌综合疗法的出现,患者的生存周期得到延长,其中新辅助化疗(neoadjuvant chemotherapy, NCT)在综合治疗中具有重要的地位^[4]。CD68作为一种细胞质蛋白,表达于巨噬细胞,因此常常作为巨噬细胞最可靠的标志物^[5]。本研究通过分析172例乳腺癌患者的临床资料,以探讨CD68和乳腺癌临床病理学特征以及NCT疗效的关系。

1 对象与方法

1.1 对象

选取2013年1月至2017年1月于南京大学医学院附属鼓楼医院收治的局部晚期乳腺癌患者作为研究对象,纳入标准:1)经病理学确诊为乳腺癌,且进行了免疫组织化学检测CD68;2)符合美国癌症联合委员会(American Joint Committee on Cancer, AJCC)第七版TNM分期^[6]中的II期或III期患者;3)病理分型均为浸润性导管癌;4)美国东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)^[7]状态评分为0~2。排除标准:1)临床资料不全的患者;2)患者肿瘤出现远处转移;3)NCT治疗前曾进行其他抗肿瘤治疗;4)NCT前患者心肾肝功能出现障碍的患者。共纳入符合要求的患者172例,年龄

27~68(中位53)岁。所有入选患者签署知情同意书, 本研究经医院伦理委员会批准展开。

1.2 NCT方法

TA方法: d1, d2静脉滴注表柔比星75 mg/m², d3静脉滴注175 mg/m², 本研究中采取此方案的患者有150例(87.21%)。TP方法: d1静脉滴注紫杉醇175 mg/m², d2静脉滴注卡铂曲线下面积(area under the curve, AUC)=4~5, 采取此方法的患者有5例(2.91%)。TCH方法: d1静脉滴注曲妥珠单抗, 首次剂量为8 mg/kg, 之后质量改为6 mg/kg, d2静脉滴注紫杉醇175 mg/m², d3静脉滴注卡铂AUC=4~5, 采取此方法的患者有17例(9.88%)。上述3种方法均每21天重复一次, 经过4周期后进行手术。

1.3 手术和辅助治疗

NCT结束1个月内进行手术, 本研究中160例采取改良根治术, 12例采取保乳术, 术后112例接受辅助放疗。其中有100例患者ER阴性, 72例患者ER阳性; 120例患者PR阳性, 52例患者PR阴性, 所有阴性患者均经内分泌治疗。

1.4 免疫组织化学判定标和分子分型标准

NCT前所有患者的病理组织由病理科全自动免疫组织机检测, 经石蜡包埋, 切成4 μm切片。然后由两位病理医师采用双盲法阅片, 按阳性细胞率及染色强度分别评分, 染色强度: 无着色为0分, 淡黄色为1分, 棕黄色为2分, 棕褐色为3分。阳性细胞率: 无阳性细胞为0分, 阳性细胞<10%为1分, 10%~50%为2分, 51%~80%为3分, 阳性细胞>80%为4分, 最后将二项评分相加即为免疫组化最终评分。其中ER判定标准^[8]: 细胞核染色≥1%即为阳性, 细胞核染色<1%为

阴性。HER2及FISH检查标准^[9]: 0≤免疫组织化学评分≤1即为阴性, ≥3为阳性, 2分再经FISH检测, 基因拷贝数扩增>2.2即为阳性。Ki-67判定标准^[10]: ≤14%为低表达, >14%为高表达。CD68判定标准^[11]: 0为阴性, ≥1为阳性; 0≤免疫组织化学评分≤4为低表达, >4为高表达。乳腺癌分子分型标准见表1。

1.5 治疗疗效判定标准

参照实体瘤疗效判定标准^[12]: 完全缓解(complete response, CR)为已知病灶完全消失且保持1个月以上; 部分缓解(partial remission, PR)为肿瘤最大单径之和减少30%以上且保持1个月以上; 疾病进展(disease progression, PD)为肿瘤最大单径之和增加20%以上或者出现了新的病灶; 稳定(stable disease, SD)为肿瘤最大单径之和减少不超过30%或者增加不超过20%且保持1个月以上。

pCR: 乳腺癌组织没有浸润性癌细胞或仅保留在原位癌的成分, 且淋巴结转移完全消失。非pCR: 乳腺癌组织有浸润性细胞成分或淋巴结转移。无病生存时间(disease-free survival, DFS): 从手术开始到局部复发、局部转移、二原发癌、远处转移或死亡时间。总生存时间(overall survival, OS): 从手术到死亡或最终随访的时间。本研究随访截止时间为2018年8月。

1.6 统计学处理

采用软件SPSS 16.0进行数据分析, CD68和乳腺癌患者临床病理学指标、其他免疫组织化学指标以及pCR分析、分子亚型和患者临床病理学指标分析均采用χ²检验, 生存分析采用Kaplan-Meier法, 多因素分析采用Cox, 相关性分析采用Spearman, P<0.05表示差异具有统计学意义。

表1 乳腺癌分子分型判定标准

Table 1 Molecular typing criteria for breast cancer

免疫组织化学指标	Luminal A型	Luminal B型	HER2过表达型	三阴性型
ER	阳性	阳性	阴性	阴性
HER2	阴性	阴性	阳性	阴性
Ki-67	≤14%	>14%	—	—

2 结果

2.1 CD68水平和乳腺癌患者临床病理学指标的关系

CD68表达和ER呈负相关($r = -0.129$, $P = 0.018$), 即CD68表达越高, ER表达越低; CD68表达和HER2($r = 0.211$, $P = 0.011$)、Ki-67($r = 0.195$, $P = 0.013$)以及肿瘤直径($r = 0.315$, $P = 0.007$)呈正相关, 即CD68水平越高, HER2和Ki-67越趋于过表达, 乳腺癌肿瘤直径越大; 而CD68和患者的年龄、绝经状况以及淋巴结是否出现转移无明显关系($P > 0.05$, 图1, 表2)。

2.2 免疫组织化学指标和pCR的关系分析

ER阴性组pCR率(25.95%)明显高于阳性组(7.81%), 差异具有统计学意义($P < 0.05$); Ki-67高表

达组pCR率(32.39%)明显高于低表达组(9.90%), 差异具有统计学意义($P < 0.05$); CD68高表达组pCR率(24.11%)明显高于低表达组(10.00%), 差异具有统计学意义($P < 0.05$, 表3)。

2.3 化疗后CD68变化趋势和pCR关系

经过化疗后, 131例(72.16%)患者CD68表达下降, 下降组的pCR率为24.43%(32/131), 未下降组(无变化或者出现上升)患者的pCR率为2.44%(1/41), 差异具有统计学意义($P < 0.05$)。

2.4 分子亚型和乳腺癌患者临床病理学指标的关系

各分子亚型和绝经状况、化疗前肿瘤直径、疗效以及化疗前CD68表达明显相关($P < 0.05$), 而与年龄、淋巴结转移不相关($P > 0.05$, 表4)。

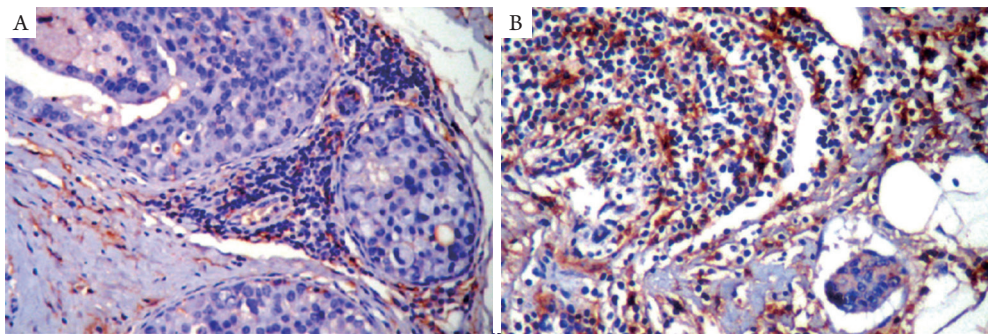


图1 免疫组织化学检测CD68在乳腺癌组织中的表达($\times 200$)

Figure 1 Immunohistochemistry of CD68 expression in breast cancer tissues ($\times 200$)

(A)低表达; (B)高表达。

(A) Low expression; (B) High expression.

表2 NCT前CD68水平和乳腺癌患者临床病理学指标的关系

Table 2 Relationship between CD68 level before NCT and clinicopathological indexes of breast cancer patients

组别	n	年龄/[例(%)]		绝经状况/[例(%)]		淋巴结转移/[例(%)]		
		>40岁	≤40岁	已绝经	未绝经	有	无	
低表达	60	48 (80.00)	12 (20.00)	42 (70.00)	18 (30.00)	51 (85.00)	9 (15.00)	
高表达	112	86 (85.71)	26 (14.29)	80 (71.43)	32 (28.57)	100 (89.29)	12 (10.71)	
χ^2		0.2345		0.0387		0.6695		
P		0.6282		0.8441		0.4132		
组别	肿瘤直径/[例(%)]		ER/[例(%)]		HER2/[例(%)]		Ki-67/[例(%)]	
	>5 cm	≤5 cm	阴性	阳性	阴性	阳性	≤14%	>14%
低表达	8 (13.33)	52 (86.67)	14 (23.33)	46 (76.67)	43 (71.67)	17 (28.34)	42 (70.00)	18 (30.00)
高表达	32 (28.57)	80 (71.43)	50 (44.64)	62 (55.36)	60 (53.57)	52 (46.23)	59 (52.68)	53 (47.32)
χ^2	5.0831		7.5935		4.0021		4.8360	
P	0.0242		0.0059		0.0454		0.0279	

表3 免疫组织化学指标和pCR的关系分析

Table 3 Analysis of the relationship between immunohistochemical indexes and pCR

免疫组织化学指标	pCR/%	χ^2	P
ER		8.5036	0.0035
阴性	25.92 (28/108)		
阳性	7.81 (5/64)		
HER2		0.0089	0.9250
阴性	19.42 (20/103)		
阳性	18.84 (13/69)		
Ki-67		13.6047	0.0002
≤14% (低表达)	9.90 (10/101)		
>14% (高表达)	32.39 (23/71)		
CD68		5.0417	0.0251
低表达	10.00 (6/60)		
高表达	24.11 (27/112)		

表4 分子亚型和乳腺癌患者临床病理学指标的关系

Table 4 Relationship between molecular subtypes and clinicopathological indexes of breast cancer patients

组别	n	年龄/[例(%)]		绝经状况/[例(%)]		化疗前肿瘤直径/[例(%)]	
		>40岁	≤40岁	已绝经	未绝经	>5 cm	≤5 cm
Luminal A型	42	28 (66.67)	7 (33.33)	34 (80.95)	8 (19.05)	5 (11.90)	37 (88.10)
Luminal B型	68	50 (73.53)	16 (26.47)	40 (58.82)	28 (41.18)	17 (25.00)	51 (75.00)
HER2过表达型	32	25 (78.13)	8 (21.87)	27 (84.38)	5 (15.62)	5 (15.63)	27 (84.37)
三阴性型	30	21 (70.00)	7 (30.00)	21 (70.00)	9 (30.00)	13 (43.33)	17 (56.67)
χ^2		0.3041		9.6977		10.9679	
P		0.9593		0.0213		0.0119	
组别	化疗前淋巴结转移/[例(%)]		疗效/[例(%)]		化疗前CD68表达/[例(%)]		
	有	有	pCR	非pCR	低表达	高表达	
Luminal A型	37 (88.10)	37 (88.10)	1 (2.38)	41 (97.62)	42 (100.00)	0 (0.00)	
Luminal B型	61 (89.71)	61 (89.71)	8 (11.76)	60 (88.24)	0 (0.00)	68 (100.00)	
HER2过表达型	28 (87.50)	28 (87.50)	11 (34.37)	21 (65.63)	8 (25.00)	24 (75.00)	
三阴性型	23 (76.67)	23 (76.67)	13 (43.33)	17 (56.67)	10 (33.33)	20 (66.67)	
χ^2	1.0582	1.0582	Fisher精确概率法		Fisher精确概率法		
P	0.7872	0.7872	<0.0001		<0.0001		

2.5 化疗前后CD68表达对DFS和OS的影响

化疗前, CD68低表达组OS和DFS均优于CD68高表达组, 差异具有统计学意义($P<0.05$; 图2, 3)。化疗后CD68下降组OS和DFS均较CD68不变或上升组延长, 差异具有统计学意义

($P<0.05$; 图4, 5)。

将化疗前Ki-67, CD68, 化疗后CD68变化, ER以及肿瘤直径纳入多因素回归分析, 结果显示化疗前Ki-67, CD68, 化疗后CD68变化是影响DFS的独立危险因素(表5)。

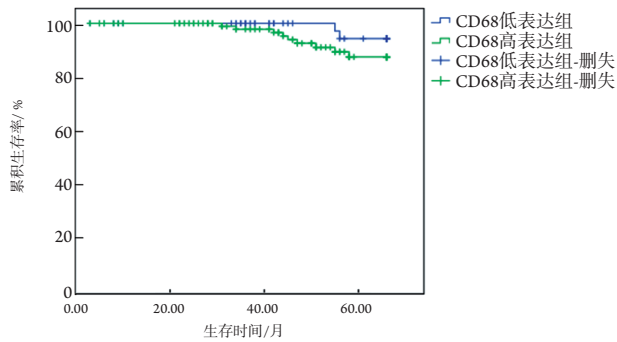


图2 化疗前CD68表达乳腺癌患者的总生存曲线

Figure 2 OS curve of breast cancer patients with CD68 expression before chemotherapy

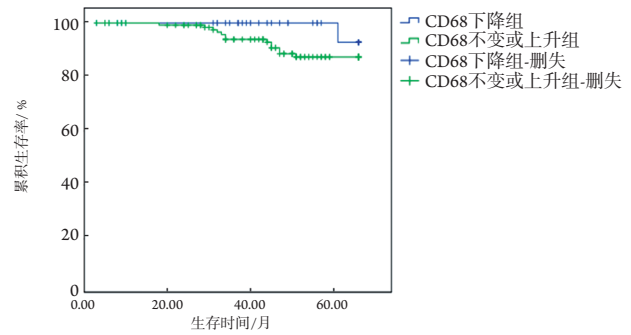


图4 化疗后CD68变化趋势的总生存曲线

Figure 4 OS curve of CD68 change trend after chemotherapy

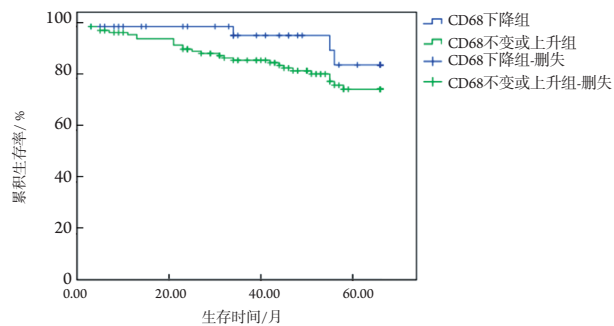


图3 化疗前CD68表达乳腺癌患者的无病生存曲线

Figure 3 DFS curve of breast cancer patients with CD68 expression before chemotherapy

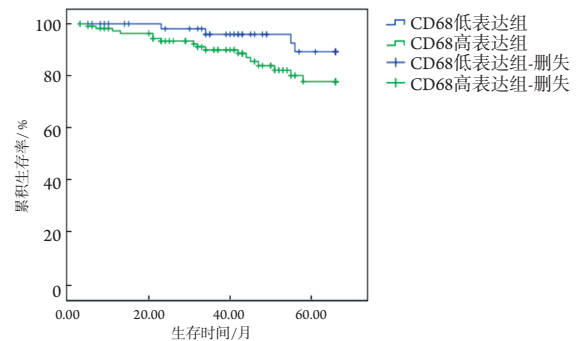


图5 化疗后CD68变化趋势的无病生存曲线

Figure 5 DFS curve of CD68 change trend after chemotherapy

表5 乳腺癌患者NCT预后危险因素的Cox分析

Table 5 Cox analysis of prognostic risk factors of NCT in breast cancer patients

因素	β	SE	Wald	P	RR	95%CI
化疗前Ki-67	-0.801	0.389	4.120	0.039	0.447	0.119~0.943
化疗前CD68	-1.015	0.344	5.602	0.026	0.397	0.184~0.883
化疗后CD68变化	-1.142	0.298	13.452	<0.001	0.109	0.097~0.439
ER	-0.119	0.364	0.109	0.745	0.893	0.502~1.648
肿瘤直径	-0.608	0.371	2.664	0.107	0.539	0.291~1.149

3 讨论

乳腺癌作为临床常见肿瘤, 是引起女性癌症相关死亡的主要原因, ER、HGR2以及Ki-67等为代表的分子分型是乳腺癌治疗和预后的判断依据, 但是乳腺癌作为一种高度异质性疾病, 即使分子分型相同, 其预后也不尽相^[13]。近些年来, 关于乳腺癌的研究不再局限于癌细胞, 肿瘤微环境作为肿瘤发生

发展的重要参与者, 也具有潜在的研究价值。肿瘤微环境包括巨噬细胞、淋巴细胞、间质干细胞、脂肪干细胞等, 其中TAMs是乳腺癌肿瘤微环境的重要组成部分, 其会通过极化成两种不同的表型(M1和M2), 参与肿瘤微环境的炎症反应^[14]。近些年来已经证实^[15]乳腺癌TAMs能够参与诱导血管生成, 帮助肿瘤细胞免疫逃逸, 以及促使免疫抑制白细胞浸润至肿瘤细胞微环境。因此基于TAMs靶向治疗

策略越来越受到关注, CD68是标记TAMs的最好标志物, 在多种肿瘤中作为预后指标, 譬如肺癌和肝细胞癌^[16-17]。

乳腺癌NCT主要用于局部晚期患者, 患者NCT后若获得pCR, 其DFS和OS均优于未达到pCR者^[18], 因此如何预测NCT疗效, 仍是目前医学工作探究的重点。本研究结果显示CD68高表达患者的pCR更高, 对化疗更为敏感, 但其DFS和OS均比低表达组要短, 差异具有统计学意义, 提示CD68高表达组近期疗效较好, 但是远期较差。CD68高表达提示乳腺癌细胞增殖活性高, 可以作为化疗敏感和判断预后的指标。有学者^[19]对10 954例乳腺癌患者进行分析, 发现Ki-67高表达和低表达患者的OS和DFS差异具有统计学意义, 提示Ki-67是乳腺癌DFS的独立危险因素。本研究显示CD68表达和Ki-67呈明显正相关, 且化疗前, CD68低表达组OS和DFS均优于CD68高表达组, 差异具有统计学意义。化疗后CD68下降组OS和DFS均较CD68不变或上升组延长, 差异具有统计学意义。化疗前多因素回归分析结果显示: Ki-67, CD68, 化疗后CD68变化是影响DFS的独立危险因素。因此化疗后CD68可以作为预后判定指标。乳腺癌分子分型作为近年来的研究热点, 在本研究中Luminal A型患者42例(24.42%), Luminal B型患者68例(39.53%), HER2过表达型患者32例(18.60%), 三阴性型患者30例(17.44%); NCT治疗后Luminal A型pCR率仅为2.28%, 明显低于其他分子亚型, 这可能是Luminal A型ER患者对化疗敏感性较差所致。

综上所述, Ki-67, ER, HGR2以及CD68是预测NCT疗效的重要指标, CD68高表达以及非Luminal A型乳腺癌对化疗更加敏感, 乳腺癌分子亚型评估能够为患者个体化治疗提供依据。

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