中晚期宫颈鳞癌患者治疗前外周血Treg计数分析

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［摘要］ **背景与目的：**中晚期宫颈鳞癌同期放化疗(concurrent chemoradiotherapy，CCRT)治疗前性价比高的疗效判断方法较有限，该研究拟通过检测治疗前外周血$CD4^+CD25^+CD127^{Low/-}$调节性T细胞(regulatory T cells，Tregs)亚群计数及血清鳞癌抗原(squamous cell carcinoma antigen，SCC-Ag)水平，评价两者预测临床疗效的可行性。**方法：**采集44例Ⅱ_B~Ⅳ_A期宫颈鳞癌患者行CCRT治疗前的外周血标本，分别利用流式细胞免疫表型分析和酶联免疫法检测外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数及血清SCC-Ag水平。收集临床和病理资料，并统计检验2个指标对疗效的预测作用。**结果：**治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数在临床有效组低于无效组［(8.78 ± 2.80)% *vs* (10.95 ± 2.56)%，$P<0.05$］，血清SCC-Ag在不同临床疗效组间差异无统计学意义，且这2个指标之间未发现相关性(Spearman'rho=-0.093，$P=0.540$)。经受试者工作特征(receiver operating characteristic，ROC)曲线确定治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg及血清SCC-Ag最佳界值分别为9.76%与9.50 ng/mL。单因素分析显示，治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数(*OR*=1.901，95%*CI*：1.112~3.219，$P=0.017$)对CCRT疗效有预测作用，而血清SCC-Ag水平无预测作用(*OR*=0.998，95%*CI*：0.001~4.253，$P=0.897$)。多因素Logistic回归分析显示，治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg为独立的临床疗效预测因子(*OR*=3.115，95%*CI*：1.253~7.742，$P=0.014$)。**结论：**治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数用于中晚期宫颈鳞癌患者CCRT临床疗效预测具有可行性。

［关键词］ 中晚期宫颈鳞状细胞癌；同期放化疗；调节性T细胞；血清鳞状细胞癌抗原

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Pre-treatment circulating regulatory T cell count analysis of advanced cervical squamous cell carcinoma patients

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［**Abstract**］ **Background and purpose:** Due to the lack of cost-effective pre-treatment predictors for advanced cervical squamous cell carcinomas treated with concurrent chemoradiotherapy (CCRT), both baseline circulating $CD4^+CD25^+CD127^{Low/-}$ regulatory T cell (Treg) count and serum squamous cell carcinoma antigen (SCC-Ag) level were measured for this feasibility study. **Methods:** Peripheral blood samples were collected from 44 patients with stage Ⅱ_B-Ⅳ_A cervical squamous carcinomas before CCRT. Flow cytometry immunophenotyping and enzyme-linked immunosorbent assay were used for circulating $CD4^+CD25^+CD127^{Low/-}$ Treg count and serum SCC-Ag level testing,

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respectively. Clinical and pathological characteristics were retrospectively reviewed to analyze the predictive value of the 2 indexes. **Results:** The baseline circulating $CD4^+CD25^+CD127^{Low/-}$ Treg count was lower in the patient group with positive treatment response than in the group with negative response ［(8.78±2.80)% *vs* (10.95±2.56)%, $P<0.05$］, and the serum SCC-Ag level showed no significant difference between the 2 groups. No correlation was detected between these 2 markers (Spearman'rho=-0.093, $P=0.540$). Determined by plotting receiver operating characteristic curves, the best cut-off points were 9.76% for circulating $CD4^+CD25^+CD127^{Low/-}$ Treg count and 9.50 ng/mL for serum SCC-Ag level, respectively. Univariate analysis showed that pretherapeutic circulating $CD4^+CD25^+CD127^{Low/-}$ Treg count (*OR*=1.901, 95%*CI*: 1.112-3.219, $P=0.017$), but not serum SCC-Ag level (*OR*=0.998, 95%*CI*: 0.001-4.253, $P=0.897$), was predictive of clinical response to CCRT. Multivariate Logistic regression analysis revealed that pre-treatment $CD4^+CD25^+CD127^{Low/-}$ Treg count was an independent predictor for clinical response to CCRT (*OR*=3.115, 95%*CI*: 1.253-7.742, $P=0.014$). **Conclusion:** Pretherapeutic circulating $CD4^+CD25^+CD127^{Low/-}$ Treg count is a feasible method to predict clinical response to CCRT in patients with advanced cervical squamous cell carcinomas.

［**Key words**］ Advanced uterine cervical squamous cell carcinoma; Concurrent chemoradiotherapy; Regulatory T cells; Serum squamous cell carcinoma antigen

同期放化疗(concurrent chemoradiotherapy，CCRT)为目前中晚期宫颈鳞癌(ⅡB期及以上)主要治疗方式之一，然而可在治疗前作疗效判断且高性价比的方法仍较有限。血清鳞状细胞癌抗原(squamous cell carcinoma antigen，SCC-Ag)水平升高见于28%~88%的宫颈鳞癌患者，是现有可反映宫颈鳞癌临床分期、肿瘤大小及播散程度等，并可用于治疗后疗效监测且较准确的肿瘤标志物[1-2]，然而治疗前血清SCC-Ag水平与临床预后的相关性却有争议[2-3]。此外，另一种简单利用流式细胞免疫表型分析计数外周血免疫细胞以评价机体免疫状态的方法也已被发现可反映多种恶性肿瘤的分期及预后[3-5]。调节性T细胞(regulatory T cells，Tregs)为具有免疫抑制效应的若干T细胞亚群，恶性肿瘤可通过诱导或招募Treg以逃脱机体免疫系统对之的监视清除。其中表型为$CD4^+CD25^+FOXP3^+$或与之相当的$CD4^+CD25^+CD127^{Low/-}$的Treg在多种恶性肿瘤患者的外周血计数高于健康人群，并与更高分期或不良疗效有关[5-8]。宫颈癌及其癌前病变中亦曾证实该亚群计数升高[9-10]，然而其与中晚期宫颈鳞癌CCRT疗效之间的关系则少有报道，本研究通过检测治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Tregs亚群计数及SCC-Ag水平，评价两者预测临床疗效的可行性。

1 材料和方法

1.1 病例收集

收集2010年9月—2011年9月在复旦大学附属肿瘤医院以顺铂为基础的CCRT治疗的中晚期宫颈鳞癌患者44例。所有患者经组织病理学确诊，初诊按国际妇产科协会(Federation International of Gynecology and Obstetrics，FIGO)分期为ⅡB及以上，治疗前未接受过抗肿瘤和免疫治疗，具有完整的临床及相关检查资料，包括治疗前外周血淋巴细胞亚群和血清SCC-Ag检测结果，疗效评价相关的影像学及体检结果等。

1.2 疗效评价

完成治疗后2年内患者每2~4个月门诊随访1次，随后调整为每2~6个月1次，疗效根据CCRT前后临床体格检查与影像学检查结果综合判断。按国际抗癌协会(Union for International Cancer Control，UICC)评定标准，疗效分为4类：肿瘤完全消失为完全缓解(complete response，CR)；肿瘤缩小达50%以上为部分缓解(partial response，PR)；肿瘤缩小不足50%或增大<25%，且无新病灶出现为疾病稳定(stable disease，SD)；肿瘤增大>25%或出现新病灶为疾病进展(progressive disease，PD)。CR或PR为临床有效，SD或PD为临床无效。

1.3 $CD4^+CD25^+CD127^{Low/-}$ Treg亚群检测

首次治疗前1天采取外周静脉血1 mL，置EDTA抗凝管送检，24 h内完成流式细胞术检测。检测抗体中CD4-FITC和CD127-PE购自美国Beckman Coulter公司，CD25-APC购自美国BD公司。流式细胞仪型号FACS CANTO Ⅱ购自美国BD公司。取全血50 μL及抗体加入BD Falcon流式进样管(12×75 mm，5 mL，购自美国BD公司)，充分混匀，避光室温温育15 min。随后加入1 mL BD FACS裂解液(购自美国BD公司)，振荡混匀后室温温育15 min以溶解红细胞，离心(500 × *g*，5 min)弃上清液。继而加入1 mL磷酸盐缓冲液(PBS)振荡混匀，离心(500 × *g*，5 min)弃上清液，其后加入50 μL PBS重悬上机检测。数据分析使用Diva软件(购自美国BD公司)，最终所获$CD4^+CD25^+CD127^{Low/-}$ Treg计数为相对计数，即占外周血$CD4^+$的淋巴细胞的百分比。

1.4 血清SCC-Ag检测

采集外周静脉血3 mL/例，使用鳞状细胞癌抗原试剂盒(购自美国雅培制药有限公司)，严格按厂方说明书进行酶联免疫法分析。检测值单位为ng/mL。

1.5 统计学处理

使用SPSS 19.0统计软件进行统计分析。不同临床疗效组外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数以均数 ± 标准差($\bar{x}\pm s$)表示，组间比较采用*t*检验。不同疗效组血清SCC-Ag水平以中位数表示，组间比较采用Mann-Whitney *U*检验。利用Spearman相关分析检验$CD4^+CD25^+CD127^{Low/-}$ Treg计数和血清SCC-Ag水平之间的相关性。构建受试者工作特征(receiver operating characteristic，ROC)曲线确立$CD4^+CD25^+CD127^{Low/-}$ Treg计数和血清SCC-Ag水平的最佳界值。采用单因素Logistic回归分析评价CCRT临床疗效的治疗前预测因子，并利用多因素Logistic回归分析识别独立的临床疗效预测因子。P<0.05为差异有统计学意义。

2 结　果

2.1 临床资料

符合研究条件中晚期宫颈鳞癌患者44例。初诊时FIGO分期为Ⅱ_B至Ⅳ_A(表1)，所有患者Karnofsky评分≥70分，年龄31~68岁，中位年龄51岁，平均年龄51.6±8.7岁。随访时间24~38个月，中位随访时间33个月。临床疗效达到CR、PR、SD和PD的患者人数分别为18、20、6和0，临床有效和无效者分别为38和6例。肿瘤大小及绝经前后患者数等见表1。

表 1　44名中晚期宫颈鳞癌患者的临床资料

Tab. 1　Clinical characteristics of 44 patients with advanced cervical squamous cell carcinomas

Characteristic	*n*(%)
Age/year	
≤51	21(47.7)
>51	23(52.3)
Menopausal status	
Premenopause	29(65.9)
Menopause	15(34.1)
Tumour size/cm	
≤4	28(63.6)
>4	11(25.0)
NA	5(11.4)
FIGO stage	
Ⅱ_B	29(65.9)
Ⅲ_A	2(4.5)
Ⅲ_B	12(27.3)
Ⅳ_A	1(2.3)
Clinical response	
CR	18(40.9)
PR	20(45.5)
SD	6(13.6)
PD	0(0)

2.2 CCRT前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数和血清SCC-Ag水平的相关性及在不同临床疗效组的分布

治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数检测值范围为5.53%~13.93%。CR组及PR组的$CD4^+CD25^+CD127^{Low/-}$ Treg计数均低于SD组，且差异有统计学意义(P<0.05，表2)，相应临床有效组$CD4^+CD25^+CD127^{Low/-}$ Treg计数也低于无效组(P<0.05，图1)。治疗前血清SCC-Ag检测值范围为0.6~151.7 ng/mL，不同临床疗效组

间差异无统计学意义。经Spearman相关分析，$CD4^+CD25^+CD127^{Low/-}$ Treg计数和血清SCC-Ag水平之间也未发现相关性(Spearman's rho=-0.095，P=0.540)。

2.3 CCRT疗效的治疗前预测因子的单因素和多因素分析

我们进一步评价治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数、血清SCC-Ag水平和其他因素(年龄、绝经与否、肿瘤大小及FIGO分期)对CCRT疗效是否有预测作用。其中治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数和血清SCC-Ag水平的最佳界值通过构建ROC曲线分别确立为9.76%和9.50 ng/mL。经单因素Logistic回归分析，治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数(P=0.017)和绝经与否(P=0.022)对CCRT疗效有预测作用，而包括治疗前血清SCC-Ag水平在内的其他因子无预测作用(P均>0.05，表3)。

建立多因素Logistic回归模型，将单因素分析中差异有统计学意义的项目纳入模型中，发现治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数(P=0.014)和绝经与否(P=0.023)均为独立的临床疗效预测因子(表3)。与治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数低组相比，计数高组(OR=3.115，95%CI：1.253~7.742)更易出现差的临床疗效，而与未绝经组患者相比，绝经组患者(OR=0.008，95%CI：0.001~0.516)更易获得好的临床疗效。

表 2 不同临床疗效组CCRT前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数及血清SCC-Ag水平

Tab. 2 Pretherapeutic circulating $CD4^+CD25^+CD127^{Low/-}$ Treg count and serum SCC-Ag level according to different clinical response to CCRT

Response to CCRT	$CD4^+CD25^+CD127^{Low/-}$ Treg ($\bar{x}\pm s$, %)	SCC-Ag (median, ng/mL)
CR	8.79±2.93	5.50
PR	8.70±2.38	10.00
SD	10.95±2.56[ab]	7.50
PD	NA	NA
Positive response	8.78±2.80	9.25
Negative response	10.95±2.56[c]	7.50

NA: Not available due to lack of patients with PD. a: Significant difference between CR and SD, P<0.05; b: Significant difference between PR and SD, P<0.05; c: Significant difference between positive and negative response, P<0.05.

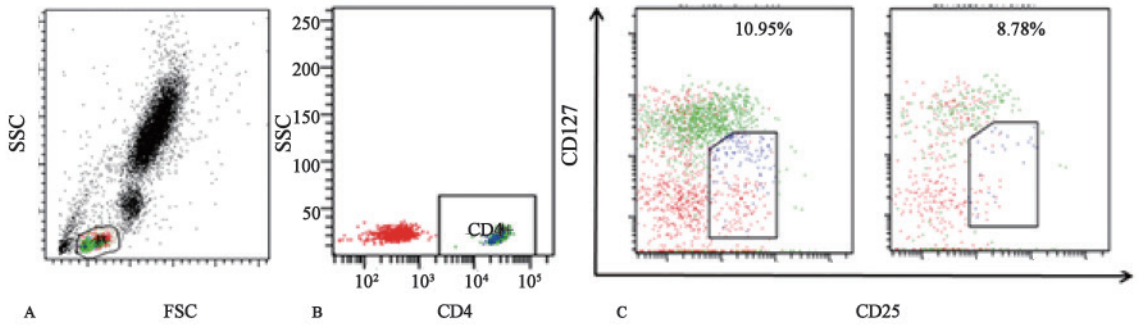

图 1 流式细胞术检测治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数

Fig. 1 Pretherapeutic circulating $CD4^+CD25^+CD127^{Low/-}$ Tregs counted by flow cytometry

A: Gating for lymphocytes; B: Gating for $CD4^+$ T lymphocytes; C: Representative $CD4^+CD25^+CD127^{Low/-}$ Treg from 2 patients with positive (right) and negative (left) clinical response, respectively.

表 3 CCRT疗效的治疗前预测因子的单因素与多因素logistic回归分析

Tab. 3 Univariate and multivariate logistic regression analysis of pretherapeutic predictors for clinical response to CCRT

Parameter	UA			MA		
	OR	95%*CI*	*P* value	*OR*	95%*CI*	*P* value
Age	0.500	0.081-3.063	0.454			
Menopause status	0.071	0.007-0.688	0.022	0.008	0.001-0.516	0.023
Tumour size	1.346	0.134-3.474	0.800			
FIGO stage	1.234	0.522-2.918	0.631			
$CD4^+CD25^+CD127^{Low/-}$ Treg	1.901	1.112-3.219	0.017	3.115	1.253-7.742	0.014
SCC-Ag	0.998	0.001-4.253	0.897			

UA: Univariate analysis; MA: Multivariate analysis.

3 讨 论

本研究结果显示，治疗前外周血$CD4^+CD25^+CD127^{Low/-}$ Treg计数对仅接受CCRT的中晚期宫颈鳞癌患者的疗效有预测作用，计数高组临床疗效倾向于更差。其机制应与$CD4^+CD25^+CD127^{Low/-}$ Treg具有抑制机体免疫监视，使恶性肿瘤发生免疫逃逸的功能有关。此外，高危型人乳头状瘤病毒(human papilloma virus，HPV)感染是宫颈癌的重要致病因素。一方面，Treg可能通过免疫抑制使HPV更不易被机体清除[11-12]。另一方面HPV可能参与了对Treg免疫抑制功能的调节[12-13]，在胸腺上皮表达HPV16 E7的转基因小鼠中，$CD4^+CD25^+$ Treg的免疫抑制活性加强[13]，而从人宫颈癌肿瘤和引流淋巴结中获得的HPV特异性$CD4^+$ Treg的免疫抑制活性也被报道依赖于HPV E6抗原[12]。

鉴于$CD4^+CD25^+$ Treg参与恶性肿瘤的发生、发展，针对该淋巴细胞亚群的免疫治疗已开始用于抗肿瘤治疗[14]，并且需要不断深入，包括对其功能的研究。事实上CD25并非该亚群的特异性标记物，可表达于所有的活化T细胞，2003年转录因子FOXP3被发现不仅对$CD4^+CD25^+$ Treg的发育具关键调控作用[15]，$CD4^+CD25^+FOXP3^+$可作为该亚群的标志物[14]。然而FOXP3表达于细胞核，流式细胞术检测需破膜处理，不可避免导致细胞固定，影响对活细胞分离功能研究的开展[7,16]。此后发现细胞膜表面抗原CD127的表达与FOXP3呈负相关，$CD4^+CD25^+CD127^{Low/-}$与$CD4^+CD25^+FOXP3^+$细胞的相关系数可高达0.96[7]，而且检测无需破膜固定，不仅利于功能研究，也更便利于临床检测的开展。因此本研究选择以$CD4^+CD25^+CD127^{Low/-}$为检测免疫表型。

对于另一项同样利用外周血检测的血清SCC-Ag水平，本研究显示治疗前该指标在临床有效和无效组间差异无统计学意义，对CCRT的疗效亦无预测作用。文献报道治疗前SCC-Ag水平能否预测宫颈癌预后有争议，无效和有效结果并存[2,17-18]，然而很多研究纳入患者包括早期宫颈癌[17-18]，而且同一研究内患者治疗方式欠统一[19-20]，在SCC-Ag水平普遍增高的Ⅱ_B~Ⅳ_A中晚期宫颈癌中，有关该指标作为预后因子研究不多，尤其对于仅接受CCRT患者的疗效预测研究鲜见报道。Yoon等[21]报道对于仅接受CCRT的Ⅰ_B~Ⅳ期的宫颈癌(虽含少量腺癌及腺鳞癌)患者，治疗前SCC-Ag水平升高组与正常组中临床有效及无效的患者比例类似，即疗效差异无统计学意义，与本研究结果相仿。更多研究显示，系列性检测治疗前后SCC-Ag水平的变化对放疗和(或)化疗有疗效预测作用[21-23]。这可能因SCC-Ag来源于鳞状上皮，其水平与鳞癌的浸润性生长方式和肿瘤大小密切相关，而后者在治疗后发生的变化是临床疗效的重要评判标准。

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