利奈唑胺相关性血小板减少

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BACKGROUND

DRUG RESISTANCE Updates

Epidemiology and characteristics of antimicrobial resistance in China

Yong-Hong Xiao[a,*], Christian G. Giske[b], Ze-Qing Wei[a], Ping Shen[a], Andreas Heddini[c], Lan-Juan Li[a]

Antimicrobial resistance in China has become a serious healthcare problem, with high resistance rates of most common bacteria to clinically important antimicrobial agents. Methicillin-resistant S. aureus, ESBL-producing Enterobacteriaceae and carbapenem-resistant Acinetobacter baumannii represent more than 50% of microbial isolates.

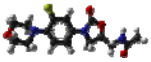
- MRSA
- VRE
- VRSA

✓ 万古霉素 vancomycin
✓ 利奈唑胺 linezolid

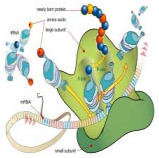
Linezolid

oxazolidinone antibiotics
- 2000 FDA
- 2007 SFDA

unique mechanism of the antibacterial action
- inhibition of protein synthesis in bacterial liposomes



approved indications for linezolid use
- vancomycin-resistant Enterococcus infection and comorbid with bacteremia
- hospital -acquired pneumonia
- complicated skin and skin structure infections
- community-acquired pneumonia and comorbid with bacteremia
- uncomplicated skin and soft tissue infections



superiority
- all ages
- liver disease
- poor kidney function
- with or without bacterial invasion of the bloodstream

Efficacy of linezolid on HAP and VAP caused by MRSA is better than vancomycin

ATS/IDSA. Am J Respir Crit Care Med. 2005;171:388-416.
ATS/IDSA(2005) guidelines for the management of adults with HAP/VAP/HCAP

血小板减少症

–来自临床的声音

安全性&耐受性

上市前临床试验
——说明书
- *腹泻/头痛/恶心/呕吐/味觉异常*
- *骨髓抑制*

血小板减少 2.4%(0.3%-10.0%)
/白细胞减少/贫血/全血细胞减少
- *乳酸酸中毒*
- *视神经病变*
- *周围神经病变*

上市后监测
——文献
- *主要的SAE是血小板减少*
- *其他国家*
  高发生率 ***(15.1-38.7%)***
- *中国*
  个案报道
  没有大样本人群的发生率

研究目的

住院患者使用利奈唑胺致相关血小板减少

? 临床实际发生率及严重程度
? 危险因素
? 风险特征的预测指标

资料&方法

回顾性研究

数据来源
- 解放军总医院 (4,000 beds)
- 使用利奈唑胺/口服/静注/序贯
- 电子医疗记录

血小板减少症评价

512 Patients were screened

–7 Patients were excluded due to younger than 18 years old

505

85 were excluded due to diagnosis and drugs
–Hematological disorders
–Chemotherapy on tumor
–Severe pancreatitis
–Hepatoblastoma
–Systemic Lupus Erythmatosus
–antiplatelet agent

425 were eligible and consented

171 were excluded due to platelet count
– baseline platelet anomalies
(less than 100×10^9/L or more than 400×10^9/L)
–initial platelets were not recorded or less than three platelet observation points

254 were included in the analysis

资料&方法

Thrombocytopenia in this study -lack of uniform diagnostic criteria

标准 1——严重

platelet count less than 100 ×10^9/L

标准 2——轻中度

25% reduction from baseline platelet count or less than 100 ×10^9/L

Variables

- ✓ Gender
- ✓ Age
- ✓ Body weight
- ✓ Daily dose (mg/kg)
- ✓ duration of linezolid administration
- ✓ laboratory data (5 factors)
  - Alanine aminotransferase
  - Total bilirubin
  - Creatinine
  - Albumin
  - Baseline platelet

结　果

研究对象概况

- 169 男性 /85 女性
- 平均年龄　59.0 ± 17.7 (range 18-95) 岁
- 平均用药时间　9.43 ± 5.63 (range 2-35.5) 天

血小板减少发生率

– 标准1	69/254	**27.2%**
– 标准 2	131/254	**51.6%**
– Ⅲ & Ⅳ 度血小板下降	27/254	**10.6%**
– 输血或输注血小板	17/254	**6.7%**

WHO assessment of acute and subacute adverse performance and indexing standards
grade Ⅲ, 26-49 × 109 / L
grade Ⅳ, ≤ 25 × 109 / L

血小板下降常见

Country	Number	Incidence	Criterion	Auther
USA	19	32%	platelet count less than 100×10^9 /L	Attassi et al
USA	48	48%	30% reduction	Orrick et al
		19%	platelet count less than 100×10^9 /L	
Janpan	42	16.7%	defined as a 100×10^9 /L decrease from the baseline or a 25% reduction	Niwa et al
Janpan	331	38.7%	defined as a 100×10^9 /L decrease from the baseline or a 30% reduction	Yoshiko takahashi et al
Chinese	254	27.2%	platelet count less than 100×10^9 /L	this study
		51.6%	defined as a 100×10^9 /L decrease from the baseline or a 25% reduction	

- ■ 结果与国外文献报道相近
- ■ 显著高于产品资料所报道的Ⅲ期临床研究结果
- ■ 轻中度血小板下降很常见（〉10%）
- ■ 存在出血倾向

结果 ——差异性分析

Risk factors Analysis of Thrombocytopenia Criterion 1

Variables	a final platelet count 〈 100×10^9/L		P value
	Patients with thrombocytopenia (n=69)	Patients without thrombocytopenia (n=185)	
Gender(male)	44(63.77%)	125(67.57%)	0.5681+
Age(years)	63.49(15.97)	57.45(18.06)	0.0152#
Weight(kg)	61.70(13.18)	65.75(13.06)	0.0294#
Alanine aminotransferase(U/L)	30.24(27.55)	35.79(47.27)	0.3084*
Total bilirubin(umol/L)	18.01(17.52)	17.76(27.30)	0.3803*
Creatinine clearance(mL/min)	84.37(63.12)	102.07(57.26)	0.0087*
Albumin(g/L)	31.34(5.27)	33.84(8.79)	0.0051*
Daily dose(mg/kg)	20.11(4.14)	18.46(4.44)	0.0016*
Baseline platelet(×109/L)	176.96(61.97)	234.14(73.68)	〈0. 0001*
Treatment duration(d)	10.52(5.01)	9.02(5.83)	0.0067*

*+ chi-square test # t-test * Mann-Whitney U-test*

结果 ——差异性分析

Risk factors Analysis of Thrombocytopenia Criterion 2

Variables	25% decrease or a final platelet count 〈 100×109/L		P value
	Patients with thrombocytopenia (n=131)	Patients without thrombocytopenia (n=123)	
Gender(male)	84(64.12%)	85(69.11%)	0.4002+
Age(years)	61.85(17.25)	56.16(17.75)	0.0102#
Weight(kg)	62.08(12.48)	67.38(13.42)	0.0013#
Alanine aminotransferase(U/L)	33.35(42.54)	35.27(43.27)	0.1388*
Total bilirubin(umol/L)	19.85(31.38)	15.63(14.94)	0.5476*
Creatinine clearance(mL/min)	85.96(58.90)	109.37(57.56)	0.0005*
Albumin(g/L)	31.77(5.10)	34.66(10.17)	0.0026*
Daily dose(mg/kg)	20.01(4.17)	17.74(4.38)	〈0. 0001*
Baseline platelet(×109/L)	212.44(76.78)	225.17(72.87)	0.1069*
Treatment duration(d)	10.35(5.79)	8.45(5.33)	0.0015*

*+ chi-square test # t-test * Mann-Whitney U-test*

结果 ——单因素分析

Risk factors for thrombocytopenia selected by logistic regression

univariate analysis

Risk factors	25% decrease or a final platelet count 〈 100×109/L			a final platelet count 〈 100×109/L		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Age(years)	1. 02	1. 00-1. 03	0. 0112	1. 02	1. 00-1. 04	0. 0165
Weight(kg)	0. 97	0. 95-0. 99	0. 0018	0. 98	0. 95-1. 00	0. 0308
Creatinine clearance(mL/min)	0. 99	0. 99-1. 00	0. 0022	0. 99	0. 99-1. 00	0. 0361
Albumin(g/L)	0. 93	0. 89-0. 98	0. 0031	0. 94	0. 89-0. 99	0. 0131
Daily dose(mg/kg)	1. 14	1. 07-1. 21	0. 0001	1. 09	1. 02-1. 16	0. 0088
Baseline platelet(×109/L)	1. 00	0. 99-1. 00	0. 1771	0. 99	0. 98-0. 99	0. 0000
Treatment duration(d)	1. 07	1. 02-1. 12	0. 0088	1. 05	1. 00-1. 10	0. 0632

Criterion 2 *Criterion 1*

结果 —多因素分析

Risk factors for thrombocytopenia selected by logistic regression

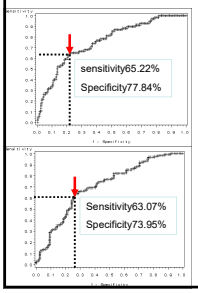
Multivariate Analysis

Risk factors	25% decrease or a final platelet count ＜100×109/L			a final platelet count ＜100×109/L		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Creatinine clearance(mL/min)	0.995	0.990-1.000	0.0351			
Albumin(g/L)	0.949	0.904-0.996	0.0323			
Daily dose(mg/kg)	1.12	1.047-1.198	0.0010	1.081	1.007-1.161	0.0308
Baseline platelet(×109/L)				0.987	0.982-0.992	0.0001
Treatment duration(d)				1.061	1.005-1.120	0.0317

Criterion 2 *Criterion 1*

结果— ROC 曲线

Clinical features of thrombocytopenia predicated by ROC curves



Criterion 1
–Youden index：0.4306
–area under ROC curve：0.757
–baseline platelet value：181×10^9 /L
–daily dose：18.75 mg/kg/d
–duration of medication：10 d

Criterion 2
–Youden index：0.3703
–area under ROC curve：0.706
–creatinine clearance：88.39 mL/min
–serum albumin：33.5 g/L
–daily dose：18.46 mg/kg/d

PLT≤ 200×10^9 /L
Ccr ≤ 30 mL/min
Ccr ≤ 50 mL/min
duration ≥14 d

每日剂量

independent risk factor for mild&severe PLT decrease

- risk increase
  - daily dose ≥18.75 mg/kg/d
  - body weight ≦ 64kg
- a protective factor of thrombocytopenia : body weight
- higher drug exposure induced thrombocytopenia

- linezolid-related thrombocytopenia is characterized as drug concentration-dependent
- dosage adjustment according to body weight may help to reduce the risk of linezolid-related thrombocytopenia in Chinese population

基线血小板

independent risk factor for severe thrombocytopenia

- baseline platelet ≤ 181×10^9/L are more likely to suffer from thrombocytopenia than others (45.9% [39/85] vs. 17.8% [30/169], *P*<0.001)
- OR=3.93，95%CI 2.24~6.90
- N=254

- Grau et al. show that thrombocytopenia is more likely to occur in patients with baseline platelet ≤ 240.7×10^9 /L (8/18, 44.4%) compared with that in other patients (4/31, 12.9%, P=0.018)
- OR=2，95%CI 0.55~7.33
- N=49

用药时间

independent risk factor for severe thrombocytopenia

- Drug instruction
  - the recommended duration : 10-14 days
  - Gerson SL et al. -prolonged use of linezolid (> 14 d) has increased the risk of thrombocytopenia 2.9% (36/1243) to 4.1% (19/461)
- ROC cut-off point (Criterion 1):10 days

- confirmed the findings of reports& drug instruction
- longer treatment need more clinical blood tests

肌苷清除率

Higher incidence in the group with severe renal impairment

- Creatinine clearance as the indicator of renal function
  - the ROC cut-off point (Criterion 2)
    creatinine clearance ≤ 88.39 mL/min
- Mild PLT decrease may occur when creatinine clearance rate is at its lower limit, while there is still no sign of renal insufficiency.
- Ccr≦30 severe renal impairment
  (48% [15/31] vs. 24% [54/222], P=0.005,OR=2.92 95%CI1.39~6.14）

- **Wu VC et al. A retrospective case-control study**
  - Two groups:end-stage or non-end-stage renal diseases
  - incidence of thrombocytopenia is higher in the group with **end-stage renal disease**
- **Brier et al. the clinical significance of accumulation of two metabolites**
  - PNU-142586
  - PMU-142300

Wu VC et al .Clin Infect Dis 2006; 42: 66-72.
Brier et al. Antimicrob Agents Chemother 2003; 47: 2775-80.

结　论

- ***Situation in Chinese patients***
  - actual incidence is much higher than in drug instructions
  - hemorrhagic tendency
- ***Risk factors***
  - low pre-treatment platelet values
  - low body weight
  - low serum albumin
  - long time of administration
  - Advanced age
  - renal impairment
- ***Predictors***
  - baseline platelet ≤ 181×10^9/L
  - daily dose ≥ 18.75 mg/kg
  - duration of linezolid therapy ≥ 10 d
- ***Strategy***
  - strengthen monitoring frequency according to risk factors
  - dosage adjustment according to body weight(PK/PD)

Thank you for your attention