PipTazo vs. Cefepime Monotherapy for Empiric Treatment of Febrile Neutropenia


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Outline

1. Review current guidelines for empiric therapy of febrile neutropenia
2. Overview of the trial
3. Primer on non-inferiority trials
4. Critical appraisal of the trial
5. Comparison to UHN Guidelines
6. Discussion
Current Guidelines
What is Febrile Neutropenia?

single oral temp \( \geq 38.3^\circ C \) or
sustained oral temp of \( \geq 38.0^\circ C \) for \( \geq 1 \)hr

AND

ANC < 500 cells/mm\(^3\) or
ANC <1000 cells/mm\(^3\) with expected
decrease to < 500 cells/mm\(^3\)
Why Do We Treat Empirically?

Empiric antibiotic therapy should be administered promptly to all neutropenic patients at the onset of fever.

Why?

- Progression of infection in neutropenics is rapid.
- Neutropenics with early bacterial infections cannot be reliably distinguished from non-infected patients.
Why Do We Treat Empirically?

- 30% of patients obtain positive cultures
  - 2/3 of these cultures are gram positive

- Always need gram negative coverage!
Causes of Febrile Episodes

**Gram-positive bacteria (60-70%)**
- S. aureus
- S. viridans
- Pneumococci
- Methicillin resistant types
  - CNST
  - VRE
  - Corynebacterium jeikeium

**Gram-negative bacilli**
- Pseudomonas
- E. coli
- Klebsiella

**Fungi**
- Candida
- Aspergillus

Fever (temperature $\geq 38.3^\circ C$) + Neutropenia ($<500$ neutrophils/mm$^3$)

- **Low risk**
  - Oral
  - Ciprofloxacin + Amoxicillin-clavulanate (adults only)

- **High risk**
  - iv
  - Vancomycin not needed

- **Vancomycin needed**

**Monotherapy**
- Cefepime, Ceftazidime, or Carbapenem

**Two Drugs**
- Aminoglycoside +
  - Antipseudomonal penicillin, Cefepime, Ceftazidime, or Carbapenem

**Vancomycin +**
- Vancomycin + Cefepime, Ceftazidime, or carbapenem
  - $\pm$ aminoglycoside

Reassess after 3–5 days
Monotherapy vs. Combo Therapy

- Combo therapy remains prominent in American guidelines

- Advantages of combo therapy?
  - Synergy against some gram negative bacilli
  - Minimize drug-resistant strains
Monotherapy vs. Combo Therapy

- Studies have shown no significant differences between monotherapy and combination therapy

Monotherapy Options

- **3rd / 4th Generation Cephalosporins**
  - Ceftazidime*
  - Cefepime

- **Carbapenems**
  - Imipenem-cilastatin
  - Meropenem

- **Piperacillin / Tazobactam?**

Trial Overview

A Randomized, Open-Label, Multicenter, Comparative Study of the Efficacy and Safety of Piperacillin-Tazobactam and Cefepime for the Empirical Treatment of Febrile Neutropenic Episodes in Patients with Hematologic Malignancies

Rationale

➢ To demonstrate the noninferiority of monotherapy with piperacillin-tazobactam compared with cefepime in the empirical treatment of febrile neutropenic patients with cancer
Design

- Open-label
- Randomized-controlled
- Multi-center (34 tertiary care hospitals)
- Multi-national (US, Canada, Australia)
- Non-inferiority trial
Design

Sample Size Calculation

- Assumed antibiotics were equally effective
- Assuming success rates of 50%,
  - needed ~132 patients per treatment group
- Assuming evaluable rate of 50%,
  - needed ~528 patients to obtain 264 evaluable patients
Design

- One-sided 95% CIs were calculated for the difference in treatment success
  - Non-inferiority was concluded if the lower bound of the 95% CI for the difference in success $\geq -0.20$
Difference in Treatment Success (New – Reference Treatment)

Design

Superior

Non-inferior

Inconclusive

-0.2 0
Intervention

PipTazo 4.5 g IV Q6H
vs
Cefepime 2 g IV Q8H

- Antibiotic prophylaxis was discontinued
- Administered for up to 21 days
- Modified at the investigator’s discretion
Inclusion Criteria

- ≥ 18 years old
- High risk for medical complications
- ANC < 0.5 x 10^9 cells/L
  - (or <1.0 x 10^9 with expected decrease to <0.5 x 10^9 after chemo)
- Febrile episode after chemotherapy for:
  - haematological malignancy
  - hematopoietic stem cell transplant (HSCT)
Exclusion Criteria

- Hypersensitivity to β-lactam antibiotics
- Hepatic dysfunction
  - bilirubin >3X ULN, transamininase > 5X ULN
- Renal insufficiency requiring dialysis
- Positive test for HIV antibody
Overall Scheme of Trial

Assessed for eligibility
\((n = 528)\)

Centralized randomization

Piperacillin-tazobactam group
Allocation to therapy, \(n = 265\)
Received allocated therapy, \(n = 265\)

Cefepime group
Allocation to therapy, \(n = 263\)
Received allocated therapy, \(n = 263\)
Primary Endpoints

“Treatment success”
- Defervescence without treatment modification
  - at 72 hours
  - end of treatment
  - test-of-cure visit
    - defined as at least 7 days post-treatment
Secondary Endpoints

- Time to defervescence
- Microbiology efficacy
- Additional use of glycopeptides antibiotics
- Emergence of resistant bacteria
- Safety
Results

- Rates of treatment success were higher among PipTazo recipients at all three assessment points:
  - 72 hours
  - End of treatment
  - Test-of-cure visit

- PipTazo was deemed to be non-inferior to cefepime at each of these time points.
## Test of Non-Inferiority

<table>
<thead>
<tr>
<th>Time of Evaluation</th>
<th>Treatment Success</th>
<th>P_{\text{inferiority}}</th>
<th>95% CI (2 sided) of the difference</th>
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<td>PipTazo (n=265)</td>
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<tr>
<td>72 hours</td>
<td>57.7%</td>
<td>48.3%</td>
<td>&lt; 0.0001</td>
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<tr>
<td>End of Treatment</td>
<td>39.6%</td>
<td>31.6%</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Test of Cure Visit</td>
<td>26.8%</td>
<td>20.5%</td>
<td>&lt; 0.0001</td>
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Difference in Treatment Success (New – Reference Treatment)

-0.2

Superior

Non-inferior

Inconclusive

Inconclusive
PipTazo - Predictor of Tx Success?

- PipTazo was associated with treatment success ONLY on multi-variate but not univariate analysis

- **univariate analysis**
  - OR 1.42, 95% CI 0.95-2.12 (CROSSES 1)
  - $\chi^2 = 2.863$, $p = 0.0914$

- **multi-variate analysis**
  - OR 1.65, 95% 1.04-2.64 (DOES NOT CROSS 1)
  - $P = 0.0354$
# Test of Superiority – Validity?

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Difference in Treatment Success (New – Reference Treatment)
Treatment Failure

- Rates of treatment failure were lower among PipTazo recipients
  - 51.7% vs 61.2%
  - OR 0.68, 95% CI 0.48-0.96 (DOES NOT CROSS 1)
  - $\chi^2 = 4.865, p = 0.027$

- Regimen medication with glycopeptides for persistent fever was the most frequent reason for treatment failure
  - Regional variability in use – effect on success rates?
Time to Defervescence

- Receipt of PipTazo was more likely to be associated with earlier defervescence
  - HR 1.24, 95% CI 1.02-1.51, p = 0.0332
Figure 2. A, Time to defervescence for all patients in the modified intent-to-treat analysis. Median times were 7 days and 10 days for the piperacillin-tazobactam and cefepime groups, respectively (P = .1058). B, Time to defervescence for modified intent-to-treat patients classified as experiencing treatment success without modification. Median times were 5 days in both groups (P = .9649). C, Time to defervescence for modified intent-to-treat patients classified as experiencing treatment failure. The median times were 9 days and 14 days for the piperacillin-tazobactam and cefepime groups, respectively (P = .0202).
Safety & Adverse Events

- Antibiotics were generally well-tolerated
- Rates of AEs were not significantly different
  - 97% vs 97.7%, p = 0.788
- More patients discontinued cefepime compared to PipTazo
  - 64 vs. 43 recipients, $\chi^2 = 5.371$, p = 0.02
- Primary reason was adverse events
  - 30 vs 19 recipients, $\chi^2 = 2.815$, p = 0.093
Safety & Adverse Events

- Reduced risk for C. difficile-associated diarrhea among PipTazo recipients
  - 2.3% vs 6.8%
  - OR 0.32, 95% CI 0.12-0.81
  - $\chi^2 = 6.381, p = 0.012$
  - STATISTICALLY SIGNIFICANT!

- Consistent with previous studies
Safety & Adverse Events

- Reduced rate of mortality among PipTazo recipients
  - 3% vs 5.7%
  - OR 0.51, 95% CI 0.21-1.24
  - $\chi^2 = 2.283$, $p = 0.131$
  - NOT STATISTICALLY SIGNIFICANT
Author’s Conclusions

- PipTazo 4.5 g IV q6h is a safe, efficacious and acceptable monotherapeutic option in the empirical treatment of high-risk febrile neutropenic patients with cancer.

- It is non-inferior compared with cefepime.
Primer on Non-Inferiority Trials
Non-Inferiority Trial Characteristics

- One-sided in nature

- Aims to demonstrate that an experimental intervention is no worse than a reference intervention by more than a prespecified amount (-\( \Delta \) to 0)

- \( \Delta \) is the “non-inferiority interval or margin”
Non-Inferiority Trial Characteristics

- Compared with classic superiority trial, null and alternative hypotheses are reversed

- 4 necessary requirements:
  1. Defined noninferiority margin
  2. Margin is accounted in sample size calculation
  3. Both intention to treat and per protocol analyses
  4. Confidence interval for the result
Non-Inferiority Interval ($\Delta$)

- Should be based on statistically reasoning, clinical judgement, and/or regulatory grounds

- Smaller than or equal to:
  - Smallest clinically meaningful difference
  - Largest clinically meaningless difference

- Should be factored into the sample size calculation
Analysis of Results

- Use BOTH intention to treat (ITT) and per protocol analyses
  - There is greater confidence in results when the conclusions are consistent
    - ITT analysis is generally biased toward finding no difference
    - Per-protocol analysis is unpredictable in terms of direction of bias
Use of Confidence Intervals

- 1-sided 97.5% CIs are often used

- 2-sided 95% CIs are recommended
  - Permits unexpected benefit of assessing superiority (if difference observed is in the opposite direction of what was expected)

- Are 1-sided 95% CIs acceptable?
Critical Appraisal
Are the Results of the Study Valid?

- Was the assignment of patients randomized?
  - Yes – central randomization

- Were all patients properly accounted for at its conclusion?
  - Few patients were lost to follow-up
  - Modified ITT analysis was conducted
Follow-Up

Piperacillin-tazobactam group
Allocation to therapy, $n = 265$
Received allocated therapy, $n = 265$

Follow-up:
- Success without modification, $n = 71$
- Initial response/regimen modified, $n = 7$
- Indeterminate, $n = 47$
- Failure, $n = 137$
- Lost to follow-up, $n = 3$
- Discontinued therapy before TOC, $n = 43$
  - Adverse event, $n = 19$
  - Insufficient response, $n = 19$
  - Protocol violation, $n = 1$
  - Withdraw consent, $n = 1$
  - Other, $n = 3$

Cefepime group
Allocation to therapy, $n = 263$
Received allocated therapy, $n = 263$

Follow-up:
- Success without modification, $n = 54$
- Initial response/regimen modified, $n = 6$
- Indeterminate, $n = 41$
- Failure, $n = 161$
- Lost to follow-up, $n = 1$
- Discontinued therapy before TOC, $n = 64$
  - Adverse event, $n = 30$
  - Insufficient response, $n = 24$
  - Protocol violation, $n = 4$
  - Withdraw consent, $n = 1$
  - Other, $n = 5$
Are the Results of the Study Valid?

- Was their blinding?
  - Open label – but differences in administration frequency would have identified antibiotics even if blinded

- Were the groups similar at the start of the trial?
  - Characteristics seems to be similar with respect to underlying disease, risk factors for infections, etc.
  - All relevant characteristics seem to have been included
Are the Results of the Study Valid?

- Were the groups treated equally?
  - Uncertain – regimens were modified at the investigator’s discretion
  - Eg. Variable vancomycin use by region
Are the Results of the Study Valid?

Was the non-inferiority margin defined a priori on the basis of statistical reasoning and clinical judgement?

- $\Delta = 0.20$ was used without justification
- Previous studies have used $\Delta = 0.10-0.20^{1-4}$
- Some studies have failed to report $\Delta$

4. Del Favero et al. CID 2001;33:1295-1301

12/09/2006 Justin Lee
Are the Results of the Study Valid?

Was the active control effect consistent with that in historical trials?

- **Success rate with cefepime = 20.5%**
  - Low compared to previous studies - 55-57%\(^1,2\)

- **Success rate with PipTazo = 26.8%**
  - Low compared to previous studies – 49-81%\(^3\)

4. Del Favero et al. CID 2001;33:1295-1301
Are the Results of the Study Valid?

- Was ITT and per protocol analysis conducted?
  - Modified ITT analysis was conducted
    - Bias towards non-inferiority
Are the Results of the Study Valid?

- Was the non-inferiority assessment adequately powered to minimize statistical uncertainty?
  - Is $\Delta = 20\%$ clinically acceptable?
    - Authors suggest that this a priori requirement had no impact on the analysis
    - PipTazo treatment success rates were as good or sometimes better than cefepime
  - Unclear whether $\Delta = 0.20$ was used in sample size calculation
Are the Results of the Study Valid?

- Was the non-inferiority assessment adequately powered to minimize statistical uncertainty?
  - What is $\Delta$’s impact on sample size?

- Given 50% success rate and $\Delta = 20\%$,
  - $2n = \left[4 \times 10.5\pi (100 - \pi)\right] / \delta^2$
  - $n = 131.25$ patients

- Given 50% success rate and $\Delta = 15\%$,
  - $2n = \left[4 \times 10.5\pi (100 - \pi)\right] / \delta^2$
  - $n = 233.33$ patients
What were the results?

- PipTazo shown to be non-inferior to cefepime using $\Delta = 0.20$
  - The lower bound of the (1 or 2 sided?) 95% CI was $\geq -0.20$

- No statistical significance
  - Superiority of PipTazo
  - Rate of any adverse event
  - Mortality

- Statistical significance in favour of PipTazo
  - Lower rates of treatment failure
    - Additional use of glycopeptides?
  - Reduced time to defervescence
  - Reduced risk of CDAD
UHN Guidelines
Day 0

Piperacillin/Tazobactam 4.5 g IV q8h plus
Tobramycin 5mg/kg IV q24h, if cultures negative after 48-72 hours, D/C Tobramycin

MODIFICATIONS:
- Severe mucositis/oral lesions
- Documented bloodstream or soft tissue infection with Gram+ organisms
- Suspected line related infection
- Abdominal/perirectal focus
- Diffuse pulmonary infiltrates
- Renal dysfunction
  (please see page 2)

Day 5-7 after antibiotic initiation

Reassessment for empiric addition of Amphotericin B 0.6mg/kg IV q24h
D/C Tobramycin when Amphotericin B started
Will the Results Help Me in Caring for my Patients?

Can the results be applied to my patients?

- Similar to UHN, trial sample focuses on patients with hematologic malignancies
  - However,
    - Excludes solid tumour
    - Includes patients with stem cell transplants and/or receiving hematological growth factors

- Differences in frequency of antibiotic administration – PipTazo dosed Q8H at UHN, not Q6H as per study
Conclusion

- Was this originally a superiority trial?
- Unclear whether $\Delta = 0.20$ is justified
- Unclear whether ability to recognize treatment effect was impaired by early modification of regimen by investigators
- Were rates of glycopeptide use significantly different?
- Does per protocol agree with the modified ITT analysis?
Conclusion

- Despite its limitations, this study makes a case for revisiting the guidelines on empirical antibiotic treatment of febrile neutropenia.
Literature on Critical Appraisal of Noninferiority Trial


Discussion