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

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

\[\text{ANC} < 500 \text{ cells/mm}^3 \] or
\[\text{ANC} < 1000 \text{ cells/mm}^3 \] with expected decrease to \( < 500 \text{ cells/mm}^3 \)

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


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Treatment Algorithm

- Fever (temperature ≥38.3°C) + Neutropenia (<500 neutrophils/mm³)

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 Options

- **3rd / 4th Generation Cephalosporins**
  - Ceftazidime*
  - Cefepime
- **Carbapenems**
  - Imipenem-cilastatin
  - Meropenem

Piperacillin / Tazobactam?


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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 ≥ -0.20

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

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>PipTazo (n=265)</th>
<th>Cefepime (n=263)</th>
<th>$P_{\text{inference}}$</th>
<th>95% CI (2 sided) of the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 hours</td>
<td></td>
<td>57.7%</td>
<td>48.3%</td>
<td>&lt; 0.0001</td>
<td>-0.013-0.139</td>
</tr>
<tr>
<td>End of Treatment</td>
<td></td>
<td>39.6%</td>
<td>31.6%</td>
<td>&lt; 0.0001</td>
<td>-0.005-0.166</td>
</tr>
<tr>
<td>Test of Cure Visit</td>
<td></td>
<td>26.8%</td>
<td>20.5%</td>
<td>&lt; 0.0001</td>
<td>-0.013-0.139</td>
</tr>
</tbody>
</table>

### Design

- Inconclusive
- Non-inferior
- Superior

Difference in Treatment Success (New – Reference Treatment): -0.2 to 0

### 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)
  - $\chi^2 = 2.863, p = 0.0914$

- **Multivariate analysis**
  - OR 1.65, 95% CI 1.04-2.64 (DOES NOT CROSS 1)
  - $P = 0.0354$

### Test of Superiority – Validity?

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<th>Time of Evaluation</th>
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<tr>
<td>72 hours</td>
<td></td>
<td>57.7%</td>
<td>48.3%</td>
<td>&lt; 0.0360</td>
<td>1.006-0.183</td>
</tr>
<tr>
<td>End of Treatment</td>
<td></td>
<td>39.6%</td>
<td>31.6%</td>
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<td>20.5%</td>
<td>&lt; 0.1108</td>
<td>-0.013-0.139</td>
</tr>
</tbody>
</table>

### 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

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
- 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

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 seem 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 $\Delta$

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4. Del Favero et al. CID 2001;33:1295-1301
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 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 ITT and per protocol analysis conducted?
  - Modified ITT analysis was conducted
    - Bias towards non-inferiority

- 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 ≥ -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 deferverscence
    - Reduced risk of CDAD

UHN Guidelines
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?

Discussion

Literature on Critical Appraisal of Noninferiority Trial