Olanzapine: Do the guidelines have it right?

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MASCC/ISOO
Annual Meeting on Supportive Care in Cancer
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Conflict of Interest Disclosure

• No conflicts
Outline

- My experience
- Why olanzapine?
- The goal is to optimize QoL in a cost-effective way, _NOT_ prevention of nausea/vomiting at all costs
- Is 10 mg sedating? (Strangely, some don’t think it is.)
- Are lower doses less sedating but also effective?
- A potential strategy for those who recognize patient concerns about sedation
My experience with olanzapine

- Prescribed routinely as a PRN for 7 years (?100 starts/yr with HEC)
- In our e-orders for AC, cisplatin for past 5 years (+ ondansetron, aprepitant, dex)
- For past 3 years all (neo)adjuvant patients receive at least one RN phone call d2-3 of C1
- I hear about EVERYTHING!
Why olanzapine as a topic?

• In MASCC-ESMO, ASCO and NCCN guidelines
• Generic but in 5/26 MASCC 2019 e-posters
• Yet many oncologists never prescribe it
Olanzapine use minimal in USA
N=23,030 AC or Cisplatin (US commercial database)

Why isn’t olanzapine always used? (speculation)

• *My patients don’t have significant nausea* (??)
• *Does it work? Hmmm, just another DRA* (??)
• Too sedating to be worth using
• Not in the chemo order system
• Patient resistance (antipsychotic according to Dr. Google)
“My patients don’t vomit with an NK₁ RA”
(cycle 1 data from 4 RCTs with AC)

- ~25% still vomit on C1
- **Nausea** more frequent (later)

“Olanzapine not that effective, poor trials”

RCTs in HEC and MEC

- Unless you are a “generic conspiracy theorist”, overwhelming evidence for efficacy

Guidelines: ASCO

Adult Patients
High-emetic-risk antineoplastic agents
• (Updated) Adult patients who are treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of a neurokinin 1 (NK₁) receptor antagonist, a serotonin (5-HT₃) receptor antagonist, dexamethasone, and olanzapine. Dexamethasone and olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

• (Updated) Adult patients who are treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK₁ receptor antagonist, a 5-HT₃ receptor antagonist, dexamethasone, and olanzapine. Olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Moderate-emetic-risk antineoplastic agents
• (Updated) Adult patients who are treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL per minute should be offered a three-drug combination of an NK₁ receptor antagonist, a 5-HT₃ receptor antagonist, and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)
- Emerging data from smaller studies and clinical practice suggests a 5 mg dose may be considered, especially for elderly or oversedated patients.
- Included as PRN option if not used upfront
Guidelines: MASCC-ESMO

The MASCC/ESMO Antiemetics Guidelines Committee has discussed the presently available published data (until June 2016) about olanzapine, which suggest that it is an effective antiemetic agent.

Olanzapine may be considered with a 5-HT₃ receptor antagonist plus dexamethasone, particularly when nausea is an issue.

(NOTE: Patient sedation may be a concern for the 10 mg dose of olanzapine. The dose used in studies has mainly been 10 mg. A lower dose may be better tolerated and as effective but further data are needed)

MASCC Level of Confidence: Low
MASCC Level of Consensus: Low
ESMO Level of Evidence: II
ESMO Grade of Recommendation: B
Guideline for Breakthrough Nausea and Vomiting

The available evidence for breakthrough nausea and vomiting suggests the use of 10 mg oral olanzapine, daily for 3 days.

(The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine.)

MASCC Level of Confidence: Moderate
MASCC Level of Consensus: Moderate
ESMO Level of Evidence: II
ESMO Grade of Recommendation: B

NOTE: No guideline was felt to be appropriate for refractory nausea and vomiting.
PRN Olanzapine vs PRN metoclopramide after fosaprepitant, palonosetron, dexamethasone

N=108

- No further episodes
  - No emesis: 31 (Metoclopramide) vs 23 (Olanzapine 10 mg)
  - No nausea: 70 (Metoclopramide) vs 68 (Olanzapine 10 mg)

Navari Support Care Cancer 2014;21:1655-63
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Guidelines summary

• 3 major guidelines recognize olanzapine
• ASCO says standard at 10 mg
• NCCN (5-10 mg) an option
• MASCC-ESMO (10 mg) may be considered
• MASCC-ESMO and NCCN offer as PRN option
• MASCC-ESMO and NCCN caution about sedation
Olanzapine and sedation

• How often is it sedating?
• Is anything other than Gr 3 sedation important?
• Are lower doses less sedating but still effective?
# Olanzapine and sedation: Frequency (10 mg)

<table>
<thead>
<tr>
<th>Author</th>
<th>% Sedation (any grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan 2009</td>
<td>73%</td>
</tr>
<tr>
<td>Yanai 2018</td>
<td>53.3%</td>
</tr>
<tr>
<td>Maeda 2016</td>
<td>73%</td>
</tr>
<tr>
<td>Babu 2016</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Mukhopadhyay 2017</td>
<td>6%</td>
</tr>
<tr>
<td>Navari 2011, 2013, 2016</td>
<td>No Gr 3 sedation</td>
</tr>
<tr>
<td>Navari 2016</td>
<td>Gr 3 in 5%</td>
</tr>
</tbody>
</table>
Is Gr 1-2 sedation important to patients?

- Not used to sedation as antiemetic side effect
- Gr 1 = present but function not limited
- Gr 2 = instrumental ADLs limited (clean house, prepare meals, manage money, use transportation)
- No studies evaluate patient’s attitudes towards sedation (in practice patients often complain)
- Is 5 mg less sedating/effective?
Olanzapine 10 mg vs 5 mg
N= 152 cisplatin DB RCT with aprepitant, DEX, 5-HT₃ RA

No evidence of inferiority of 5 mg but another large study needed

Yanai Int J Clin Oncol 2018;23:382
Not surprisingly, a lower dose is less sedating

Yanai  Int J Clin Oncol 2018;23:382
Olanzapine 5 mg vs Placebo
N= 44 HEC/MEC with aprepitant, DEX, 5-HT3 RA

- ++ small, ++ heterogeneous
- Need much larger study
- And MASCC 2019 had it

Mizukami J Pain Symptom Manage 2014;47:542
Japanese J-FORCE Study

- Best study by far to evaluate 5 mg dose
- N=710
- Cisplatin $\geq 50$ mg/m$^2$
- Randomized, double blind, placebo controlled
- Stratified by gender, cisplatin dose, age
- Std therapy was dex, aprepitant, palonosetron
- Placebo vs 5 mg olanzapine d1-4

Abe MASCC 2019 e-poster
Olanzapine 5 mg vs Placebo

% CR

94.9 88.6 79.1 65.8 78 63.5

P<0.001

Acute  Delayed  Overall

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Japanese J-FORCE Study

- Superiority in CR similar to absolute differences in meta-analyses of 5-HT$_3$ RA, dex and NK$_1$ RA
- Somnolence in 43.1% vs 33% (placebo)
  - ? Fatigue not distinguishable from sedation?
Does it work when started cycle 2?

- No randomized trials, just observational data
- Addition of 2.5 mg\(^1\), 5 mg\(^2\) 5-10 mg\(^3\) and 10 mg\(^4\) on cycle 2 reported C2 benefit after poor C1 results
- Fits with similar observations with DEX, 5-HT\(_3\) RA and NK\(_1\) RA

3 Chiu Ann Pall Med 2016;5:172 4 Mehra Meical Oncology 2018;35:12
Nausea with HEC is not universal

- Goal is optimal QoL, **not** control of n/v
- Many with nausea will not take PRN
- With aprepitant, ondansetron, dexamethasone

  **NO** nausea  No sig nausea (VAS ≤ 25 mm)

- AC$^1$  33%  61%
- Cisplatin$^2$  48%  72%

- Is it wise to sedate a majority when a substantial number are free of nausea?

Olanzapine: a practical approach

• “Triple therapy” – 1/3 to 1/2 have no nausea
• Some very annoyed by sedation @ even 2.5 mg
• Olanzapine effective upfront, as a PRN and as a salvage medication (for subsequent cycles)
• Sedation usual with 10 mg, less so with 5 mg
• To optimize QoL, perhaps the best approach is NOT to premedicate with olanzapine for cycle 1
My strategy for HEC to optimize QoL

Cycle 1:
Olanz 2.5 mg bid PRN + 5-HT₃ RA + NK₁ RA + Dex

No nausea
Unused, no sedation

- Olanz effective, no sedation

- Olanz effective, sedation → ½ tab bid

- Olanz ineffective, no sedation* → 7.5-10 mg/d

- Olanz ineffective, sedation* → induce tolerance by ½ tab dosing 4 days pre C2

*Consider other causes especially gastric reflux
Conclusions

• OVERWHELMING evidence for efficacy → Olanzapine deserves to be in guidelines

• Sedation VERY common with 10 mg

• Lower doses less sedating; effective but not established as equivalent to 10 mg

• Need more data about dose-response (efficacy, sedation) and patient acceptability of sedation
Thank you! See you in Toronto for MASCC 2022