CONTROLLING DISEASE AND TREATMENT SIDE-EFFECTS: ABSTRACTS 1550PD AND 1551PD

Discussant:

Fausto Roila
Medical Oncology, Terni, Italy
CONFLICT OF INTEREST: DISCLOSURE

- I am a member of the Advisory Board on aprepitant for MSD

- I have been a speaker for MSD Italy on the prophylaxis of chemotherapy-induced emesis

- I am conducting research sponsored by MSD on the prophylaxis of emesis with aprepitant
Aprepitant is active in the management of biological therapies - related severe pruritus: A phase II study

Daniele Santini
d.santini@unicampus.it

Department of Medical Oncology
Università Campus Bio-Medico, Rome, Italy
PRURITUS IN EGFR TREATED PTS

• Occurs in approximately half of the pts

• Pruritus rarely requires dose modifications or discontinuation of drug therapy BUT can have dramatic impact on quality of life

• Papulopustular (acneiform) rash (25-90% of pts) and xerosis (12-35% of pts) induced by EGFR inhibitors could induce pruritus.
PRURITUS IN EGFR TREATED PTS

- Neurotransmitters involved are not clearly elucidated (histamine yes; serotonin, opioids, and gamma-aminobutyric acid, substance P receptors: unknown)

- No controlled clinical studies yet published to evaluate the optimal therapy for EGFR-I-induced pruritus (much of the data originated from case series as well as case reports)
PRURITUS TREATMENT

• Non-sedating second-generation antihistamines (i.e., loratadine) are recommended during daytime.

• For patients who suffer from nighttime pruritus, first generation antihistamines (such as diphenhydramine and hydroxyzine) are preferable.

• Antiepileptic agents, such as pregabalin and gabapentin, are reported to provide pruritic relief in the general patient population.
Aprepitant in the treatment of severe pruritus

Rationale

- Biologic Therapy with EGFR\TKI inhibitor induces the secretion of stem-cell factor and the subsequent accumulation of dermal mast cells in the lesional skin of patients with biologic therapy-induced rash.
- SP activates mast cells through the neurokinin-1 receptor and causes the release of pruritogens.
- Aprepitant is an oral neurokinin-1–receptor antagonist and blocks the mast-cell degranulation mediated by the neurokinin-1 receptor.

Modified from Gerber PA et al. NEJM, 2011
PRURITUS TREATMENT

• Recently, aprepitant, an NK-1 antagonist, was reported to reduce pruritus that is caused by erlotinib \((Vincenzi \, B \, et \, al, \, N \, Engl \, J \, Med \, 2010; \, 363: \, 397-8)\) and pruritus sine materia in 2 cancer pts submitted to CT \((Vincenzi \, B \, et \, al, \, Support \, Care \, Cancer \, 2010; \, 18: \, 1229-30)\).

• Possible drug–drug interactions (aprepitant is a CYP3A4 inhibitor) with EGFR inhibitors (especially gefitinib, but also erlotinib).
SANTINI’S’ STUDY

• phase II study evaluating the effects of aprepitant in managing biological therapy-induced pruritus

• 45 pts with severe pruritus (VAS score ≥ 7): 24 refractory to standard treatment and 21 untreated

• Pts with refractory pruritus receive at least 1 week of steroids and/or antihistaminics. Both groups received aprepitant 125 mg on day 1 and 80 mg on day 3 and 5
RESULTS

• 16 pts received erlotinib, 23 cetuximab, 1 lapatinib, 3 sunitinib, 1 imatinib and 1 gefitinib.

• The median decrease in pruritus intensity at 1 week was 93% in the refractory group and 100% in the naive group.

• Aprepitant was active regardless of the type of biological therapy. Only 6 pts presented pruritus recurrence (after a median of 7 week).

• No toxic effect of aprepitant.
Resistant group

P < 0.0001

VAS score

Baseline
After standard therapy
After Aprepitant
Naive group

P < 0.0001

Baseline

After Aprepitant

VAS score
COMMENTS

• This is an interesting study which shows the activity of aprepitant against pruritus induced by different types of biological therapies and in different pts (untreated and with refractory severe pruritus)

• Randomized controlled trials in a larger patient population have to be carried out to define the efficacy, safety and the place in therapy of aprepitant

• A registrative study sponsored by the pharmaceutical company marketing aprepitant could be wellcome
ROLE OF TEMPORARY OVARIAN SUPPRESSION OBTAINED WITH GnRH ANALOG IN REDUCING PREMATURE OVARIAN FAILURE INDUCED BY CHEMOTHERAPY IN PREMENOPAUSAL CANCER PATIENTS: A METANALYSIS OF RANDOMIZED STUDIES

CT-INDUCED PREMATURE OVARIAN FAILURE (POF)

• Premenopausal cancer patients treated with CT are at risk of POF with:
  - loss of fertility
  - subjective (hot flashes, sweats, loss of libido)
  - objective (i.e; osteoporosis, cardiovascular incidents, cognitive dysfunction, genital atrophy) menopausal symptoms
CT-INDUCED PREMATURE OVARIAN FAILURE (POF)

- POF risk influenced by age, CT type and duration

- No standard strategies for preventing chemotherapy-induced ovarian failure are yet available

- Several phase II studies seem to suggest the use of GnRH analogs to prevent POF
GnRH ANALOGS TO PREVENT POF

• ASCO recommendations on fertility preservation in cancer pts (Lee SJ, et al. J Clin Oncol 2006; 24: 2917-31) state that ovarian suppression through GnRH agonist or antagonist during CT is a highly controversial method to maintain fertility

• This recommendation was based on small randomized studies and case series
GnRH ANALOGS TO PREVENT POF

• Cochrane’s review (2011) which included 4 RCT enrolling 154 pts showed that GnRH agonists was effective in protecting menstruation (RR 1.90) and ovulation (RR 2.70) after chemotherapy although no significant difference in pregnancy rates was shown (Chen H, et al. Cochrane Database Syst Rev. 2011 Nov 9; (11):CD008018. Review)

• The use of GnRH should be considered in protecting ovaries during CT although large and well-designed RCT should be conducted to clarify the efficacy and safety of GnRH agonists
GnRH ANALOGS TO PREVENT POF

- At least 4 other important studies (all in breast cancer pts) have been published after the Cochrane review, three negatives and one positive:

- 60 estrogen receptor negative pts received anthracyclines plus cyclophosphamide (± taxane)-CT ± goserelin. Resumption of normal ovarian function 6 months after CT was observed in 70% and 57% of pts (a non-significant difference) (Gerber B, J Clin Oncol 2011; 29: 2334-41).
GnRH ANALOGS TO PREVENT POF

- 49 pts received AC, AC followed by paclitaxel or FEC ± triptorelin. Resumption of menses was observed in (88% and 90% of pts, a not significant difference) (Munster PN, J Clin Oncol 2012; 30: 533-38).

- 227 pts randomized to receive CT ± goserelín. There were no significant differences in ovarian protection but results are still preliminary (Leonard RC, J Clin Oncol 2010; 28: 89s, abstr. 590).
GnRH ANALOGS TO PREVENT POF

- 281 pts received adjuvant or neoadjuvant anthracyclines based-, anthracyclines + taxane- or CMF-CT ± triptorelin. The rate of early menopause (no menses and post-menopausal levels of FSH for 1 year after the end of CT) was 25.9% and 8.9% while resumption of menses was observed in 63.3% and 49.6% of pts (both statistically significant differences) (Del Mastro L, JAMA 2011; 306: 269-76)
DEL MASTRO’S STUDY

• A metanalysis of randomized studies evaluating the role of temporary ovarian suppression with GnRH analogs in reducing POF

• 8 RCT involving 803 premenopausal women randomly assigned to receive CT± GnRH analogs have been included (6 study in breast cancer and 2 in lymphoma patients)
METHODS

Outcomes of analysis

The outcome analyzed was the occurrence of POF after the end of chemotherapy. The effect of the treatment in terms of POF was expressed as a OR of the GnRH analogue plus chemotherapy arm over the standard chemotherapy without GnRH analogue arm. Thus an OR <1 favors the GnRh analogue plus chemotherapy treatment, indicating a lower probability of POF occurrence.
Effect of GnRH analogues on risk of POF

<table>
<thead>
<tr>
<th>Study</th>
<th>ID</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badawy</td>
<td></td>
<td>0.06 (0.02, 0.20)</td>
</tr>
<tr>
<td>Sverrisdottir_1</td>
<td></td>
<td>0.19 (0.04, 1.06)</td>
</tr>
<tr>
<td>Sverrisdottir_2</td>
<td></td>
<td>2.03 (0.31, 13.27)</td>
</tr>
<tr>
<td>Behringer*</td>
<td></td>
<td>0.22 (0.02, 2.67)</td>
</tr>
<tr>
<td>Leonard</td>
<td></td>
<td>1.31 (0.66, 2.60)</td>
</tr>
<tr>
<td>Del Mastro</td>
<td></td>
<td>0.25 (0.12, 0.52)</td>
</tr>
<tr>
<td>Gerber</td>
<td></td>
<td>0.56 (0.19, 1.62)</td>
</tr>
<tr>
<td>Demeestere*</td>
<td></td>
<td>1.14 (0.38, 3.42)</td>
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<tr>
<td>Munster</td>
<td></td>
<td>1.24 (0.19, 8.20)</td>
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<tr>
<td>Overall (I-squared = 73.2%, p = 0.000)</td>
<td></td>
<td>0.49 (0.35, 0.69)</td>
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* Lymphomas

Heterogeneity chi-squared = 29.82; p = 0.000
CONCLUSIONS

Our meta-analysis shows that GnRH analogues significantly reduce the risk of POF in premenopausal breast cancer and lymphoma patients. However, the significant heterogeneity among trials indicates that additional studies are needed to confirm the beneficial effect of GnRH analogues.
• This is an important study showing that GnRH analogs protect more pts by POF.

• Many problems remain to be defined with the use of GnRH analogs:
  1) the long-term maintenance of ovarian function
  2) the preservation of fertility

  these studies should have a longer follow-up duration
3) the interaction of GnRH with CT (even if we know that there are no differences in outcomes in at least 3 RCT between CT ± ovarian suppression).

4) the possible detrimental effect of the lack of CT-induced amenorrhea on the outcome (CT-induced amenorrhea is associated with an improved prognosis)

Studies should report the 5-year OS to evaluate the antitumoral effect