Neoadjuvant Paclitaxel Poliglumex (PPX), Cisplatin, and Radiation (RT) for Esophageal Cancer

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BACKGROUND

Chemotherapy/Radiation
- In phase 3 trials, the pathologic complete response rate with chemotherapy/radiation in patients with esophageal adenocarcinoma is approximately 15%.
- The rate of grade 3/4 esophagitis with 5-FU/cisplatin/radiation in esophageal cancer is approximately 40%.

Paclitaxel Poliglumex (PPX)
- Paclitaxel poliglumex (PPX) is a macromolecular drug conjugate that links paclitaxel to a biodegradable polymer, poly-L-glutamic acid.
- PPX is water-soluble, eliminating the need for Cremophor EL or other solvents.
- PPX has a molecular weight of 40,000 as compared to 854 for paclitaxel.
- PPX has demonstrated tumor tissue radiation enhancement factors from 4.0 to 8.0.

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PPX Clinical Trials
- Prior phase 1 studies of PPX/RT in esophageal cancer were performed by the Brown University Oncology Group.
  - Phase 1 PPX/RT – MTD: PPX 70 mg/m²/week for 6 weeks with 50.4 Gy concurrent RT.
  - Phase 1 PPX/Cisplatin/RT – MTD: PPX 50 mg/m²/week with cisplatin 25 mg/m²/week for 6 weeks with 50.4 Gy concurrent RT.
  - Dose-limiting toxicities – esophagitis, nausea, dehydration

Dose-Limiting Toxicities in Phase 1 Study of PPX/RT

Toxicities 2 Grade 2 in Phase 1 Study of PPX/RT

<table>
<thead>
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<th>No. Patients (n = 21)</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<td>Esophagitis/gastritis</td>
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<td>Thrombocytopenia</td>
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METHODS

Eligibility Criteria
- Adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction
- Potentially resectable disease
- Regional adenopathy allowed
- No evidence of distant organ metastases
- Adequate hematologic, renal, and liver function

Study Objectives
- To determine the pathologic complete response rate of neoadjuvant PPX, cisplatin, and concurrent radiation
- To evaluate the toxicities of neoadjuvant PPX, cisplatin, and concurrent radiation

Study Design
- Single-arm phase 2 study

PPX
- 40 Patients (50 mg/m² Days 1,8,15,22,29,36)

Cisplatin
- (75 mg/m² Days 1,8,15,22,29,36)

Radiation
- (50.4 Gy) (4 Gy/day 1-25, 28-33, 36-39)

RESULTS

Patient Characteristics
- N = 40
- Median age, years (range) 62 (30-81)
- Male 33
- Female 7
- Tumor type, n
  - Esophageal 35
  - Gastric 5
- Pathology, n
  - Adenocarcinoma 37
  - Squamous cell carcinoma 3

Response
- Three of 40 patients (7.5%) achieved a complete clinical endoscopic response and refused surgery.
- Two patients had squamous cell carcinoma and 1 had adenocarcinoma.
- Twelve of the 37 patients who underwent surgery (32%) achieved a pathologic complete response. All 12 patients had adenocarcinoma.
- There was 1 surgical death due to multisystem organ failure.

Survival
- It is too early to assess survival data.

Toxicities
- There were no treatment-related deaths.
- Only 1 patient required a feeding tube and 1 patient used total parenteral nutrition.

SUMMARY AND CONCLUSIONS

- PPX, cisplatin, and concurrent radiation is a well tolerated, easily administered regimen for esophageal cancer.
- A low incidence of significant esophagitis was observed.
- The regimen demonstrated a high pathologic complete response rate.
- A phase 3 trial comparing this regimen to 5-FU/Cisplatin/Radiation is in the planning phase.
- Substantial preliminary activity was demonstrated in this phase 1 study with one-third of patients undergoing a complete clinical response to PPX/RT alone.

REFERENCES