Phase III Trail of perioperative alone compared with perioperative plus postoperative antimicrobial prophylaxis in gastric cancer surgery (OGSG0501)

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Summery

- **Purpose:** The aim of this phase III study was to investigate non-inferiority of perioperative antimicrobial prophylaxis (AMP) alone to perioperative plus postoperative AMP for prevention of surgical-site infection (SSI) in gastric cancer surgery.
- **Methods:** Between June 2005 and December 2007, patients with gastric cancer, which was curable by distal gastrectomy, were randomly assigned to perioperative AMP (cefazolin (CEZ) 1g, at <30min before incision, every 3h intraoperative supplements) plus postoperative AMP (CEZ 1g, twice daily for 2 postoperative days) (Peri/Post AMP) or perioperative AMP alone (Peri AMP). The primary endpoint was the incidence of SSI. With 171 patients per arm, this study had 80% power to demonstrate non-inferiority with 5% margin of Peri AMP alone and 0.05 1-sided alpha.
- **Results:** 355 patients were enrolled (Peri/Post AMP: 179, Peri AMP:176) in 7 centers. The SSI rate was 8.9% (16 of 179) for Peri/Post AMP and 4.5% (8 of 176) for Peri AMP, with no significant differences (Fisher's exact test: P=0.14, RR=1.98 [95%CI, 0.98-4.44], but showing a significant non-inferiority (P<0.001). There was no differentiation in the class of SSIs, the incidence of remote site infections, pyrexia in excess of 38 degrees, and the length of postoperative hospital stay.
- **Conclusions:** These results suggest that perioperative AMP is sufficient for patients with gastric cancer undergoing distal gastrectomy.

Introduction

- According to the Centers for Disease Control (CDC) guidelines for the prevention of surgical site infections (SSIs), a first generation cephem or penicillin as antimicrobial prophylaxis (AMP) should be administered for clean or clean-contaminated operations. Administration of AMP within 30 minutes of the first surgical incision with intraoperative supplemental administration every three or four hours and postoperative administration for 24 hours or less are the recommended timings and durations for the administration of AMP.
- On the contrary in Japan, according to guidelines developed by the Japanese Society of Chemotherapy (JSC) for the prevention of SSI, three to four days after the operation is an appropriate duration for the administration of AMP for clean-contaminated operations. The justification given for this is that in Japan a wider area of lymphadenectomy is performed for malignant tumors of the upper gastrointestinal tract when compared with those performed in America and European countries.

Purpose

- We have shown that administration of AMP within 30 minutes of the first surgical incision and supplemental administration of AMP every three hours before skin closure may be enough to keep the incidence of SSI low by multicenter phase II study: OGSG0202.
- The aim of this present study was to investigate non-inferiority of perioperative antimicrobial prophylaxis (AMP) alone to perioperative plus postoperative AMP for prevention of surgical-site infection (SSI) in gastric cancer surgery.

Methods

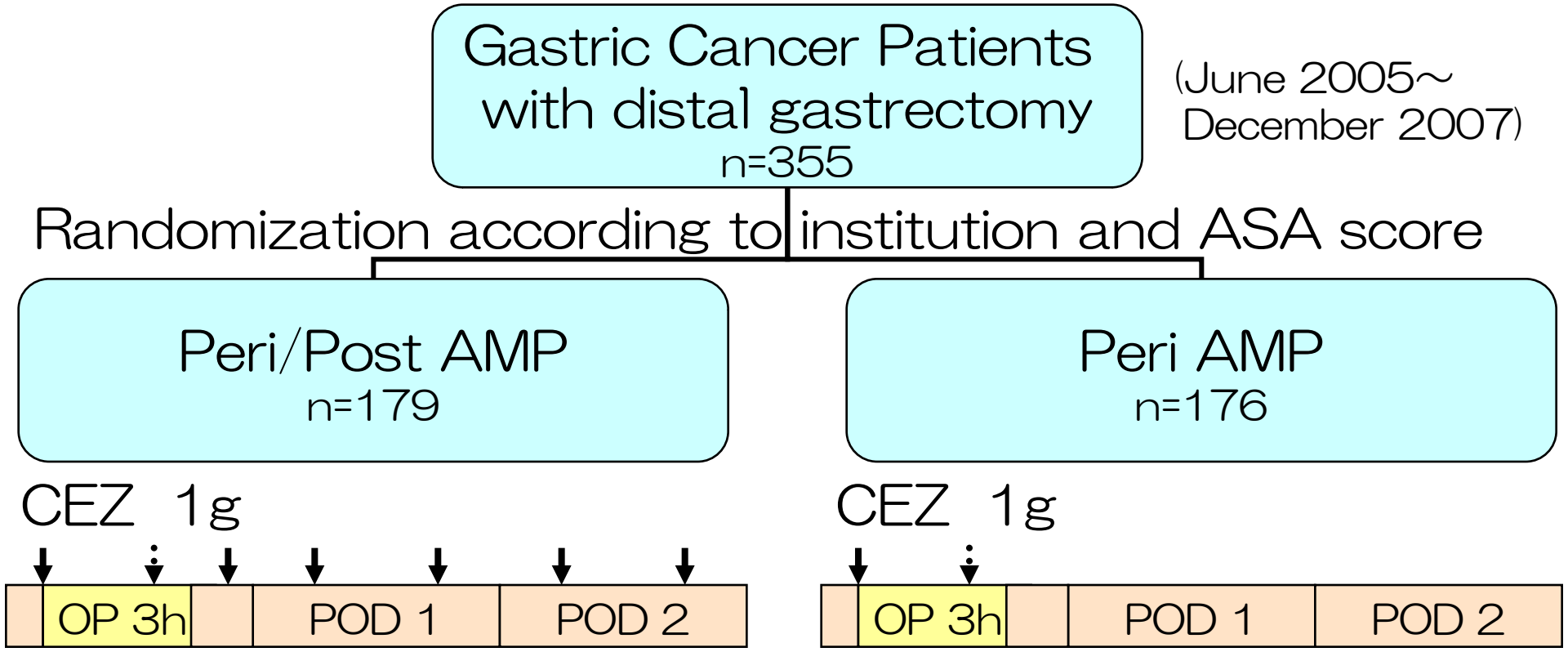
- Study Design　A multicenter phase III study.
  Primary endpoint: the incidence of SSI.
  Secondary endpoints: the class of SSIs, the incidence of remote site infections, pyrexia in excess of 38 degrees, and the length of postoperative hospital stay.
- Randomization and statistical analyses
  Between 06/2005 and 11/2007, 355 patients with gastric cancer, which was curable by distal gastrectomy, were enrolled.
  The patients were randomly assigned preoperatively to perioperative AMP (cefazolin (CEZ) 1g, at <30min before incision, every 3h intraoperative supplements) plus postoperative AMP (CEZ 1g, twice daily for 2 postoperative days) (Peri/Post AMP) or perioperative AMP alone (Peri AMP) with minimization method, according to institution and American Society of Anesthesiologists (ASA) score.
  With 171 patients per arm, this study had 80% power to demonstrate non-inferiority with 5% margin of Peri AMP alone and 0.05 1-sided alpha. A P value <0.05 was considered to indicate statistical significance.

Eligibility

Patients were included in the study if they met the following eligibility criteria.

1. The informed consent process was completed.
2. Histologically proven gastric cancer which was curable by distal gastrectomy with D2 lymphadenectomy at preoperative diagnosis.
3. Distal gastrectomy which was classified as a clean-contaminated operation.
4. An American Society of Anesthesiologists (ASA) score of 1 or 2.
5. None of the following conditions were permitted:
   - Active or uncontrolled infection;
   - Neoadjuvant chemotherapy;
   - The occurrence of secondary malignancy;
   - Administration of steroids.

Schema



- Primary endpoint: the incidence of SSI.
- Secondary endpoints: the class of SSIs, the incidence of remote site infections, pyrexia in excess of 38 degrees, and the length of postoperative hospital stay.
- This study had 80% power to demonstrate non-inferiority with 5% margin of Peri AMP alone and 0.05 1-sided alpha.

Preoperative demographic characteristics

	Peri/Post AMP (n=179)	Peri AMP (n=176)
Median age (range)	65 (35-84)	66 (36-84)
Sex		
Male	125	115
Female	54	61
ASA score		
1	123	122
2	56	54

Intraoperative demographic characteristics

	Peri/Post AMP (n=179)	Peri AMP (n=176)
Mean operative time (min)	200 (64-415)	209 (54-428)
Intraoperative blood loss	210 (0-1700)	200 (0-880)
Intraoperative Transfusion		
Yes / No	5 / 174	0 / 176
Extent of lymph node dissection		
D0 or D1 / D2	59 / 119	53 / 123
Reconstructive methods		
Billroth I	95	79
Roux-Y	74	90
Others	10	7
Anastomotic methods		
Hand-sewn	34	21
Auto- suture	119	119
Mixed	26	36
Presence of drainage tube		
Yes / No	26 / 153	19 / 157

Infections and other some complications after operation

	Peri/Post AMP (n=179)	Peri AMP (n=176)	P Risk ratio (CI 95%)
SSI			
Not detected	163 (91.1%)	168 (95.5%)	P=0.138 RR=1.98 (0.89-4.44)
Detected	16 (8.9%)	8 (4.5%)	
Superficial or deep incisional	5	2	
Organ/space	11	6	
Remote site infection			
Not detected	173 (96.6%)	167 (94.9%)	P=0.441 RR=0.66 (0.25-1.70)
Detected	6 (3.4%)	9 (5.1%)	
Pyrexia more than 38℃			
Not detected	127 (71.8%)	116 (65.9%)	P=0.361 RR=0.86 (0.63-1.16)
Detected	52 (29.2%)	60 (34.1%)	
Anastomotic leakage			
Not detected	175	175	P=0.371 RR=0.3.96 (0.60-26.3)
Detected	4	1	
The length of hospital stay (days)	14.8±9.6	15.2±12.0	P=0.697

Results

- 355 patients were enrolled (Peri/Post AMP: 179, Peri AMP:176) in 7 centers.
- The SSI rate was 8.9% (16 of 179) for Peri/Post AMP and 4.5% (8 of 176) for Peri AMP, with no significant differences (Fisher's exact test: P=0.14, RR=1.98 [95%CI, 0.98-4.44], but showing a significant non-inferiority (P<0.001).
- The remote site infection rate was 3.4% (6 of 179) for Peri/Post AMP and 5.1% (9 of 176) for Peri AMP, with no significant differences (P=0.44, RR=0.66 [95%CI, 0.25-1.70]).
- The rate of Pyrexia more than 38℃ was 29.2% (52 of 179) for Peri/Post AMP and 32.1% (60 of 176) for Peri AMP, with no significant differences (P=0.36, RR=0.86 [95%CI, 0.63-1.16]).
- The length of postoperative hospital stay was 14.8±9.6 days for Peri/Post AMP and 15.2±12.0 days for Peri AMP, with no significant differences (P=0.69).

Conclusions

- This study shows that perioperative AMP, i.e. administration of AMP within 30 minutes of the first surgical incision and supplemental administration of AMP every three hours before skin closure, is sufficient for clean-contaminated operations like distal gastrectomy for gastric cancer in Japan.
- Similar studies are required to clarify for patients undergoing total gastrectomy and/or Western patients undergoing gastric cancer surgery, who generally have more co-morbidity.

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Methods: Between June 2005 and December 2007, patients with gastric cancer, which was curable by distal gastrectomy, were randomly assigned to perioperative AMP (cefazolin (CEZ) 1g, at <30min before incision, every 3h intraoperative supplements) plus postoperative AMP (CEZ 1g, twice daily for 2 postoperative days) (Peri/Post AMP) or perioperative AMP alone (Peri AMP). The primary endpoint was the incidence of SSI. With 171 patients per arm, this study had 80% power to demonstrate non-inferiority with 5% margin of Peri AMP alone and 0.05 1-sided alpha.

Results: 355 patients were enrolled (Peri/Post AMP: 179, Peri AMP:176) in 7 centers. The SSI rate was 9.0% (16 of 178) for Peri/Post AMP and 4.5% (8 of 176) for Peri AMP, with no significant differences (Fisher's exact test: P=0.14, RR=1.98 [95%CI, 0.98-4.44], but showing a significant non-inferiority (P<0.001). The remote site infection rate was 3.4% (6 of 178) for Peri/Post AMP and 5.1% (9 of 175) for Peri AMP, with no significant differences (P=0.44, RR=0.66 [95%CI, 0.25-1.70]).

Conclusions: These results suggest that perioperative AMP is sufficient for patients with gastric cancer undergoing distal gastrectomy.