MULTICENTER PROSPECTIVE STUDY ON THE EFFICACY AND SAFETY OF DENOSUMAB IN GASTROINTESTINAL CANCER PATIENTS RECEIVING SHORT-TERM PERIODIC STEROID PREMEDIATION FOR PREVENTION OF CINV. (ESPRESSO-02/HGCSG1602)

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Background

- ✓ Bone health and the management of treatment-related bone loss are important for cancer care, as bone loss may lead to osteoporosis and its complications, including fractures, pain, and diminished quality of life (QOL)¹⁻³.
- ✓ We previously reported that short-term periodic premedication of glucocorticoids (GCs) used with chemotherapy for gastrointestinal cancer (GIC) caused the reduction of bone mineral densities (BMD) and the increase of serum bone alkaline phosphatase (BAP) (Fig.1 ESPRESSO-01 study⁴; Oncologist 2017;22(5):592-600).

- ✓ Surprisingly, it seems that the BMD decreasing levels due to only the 16-week GC usage in GIC chemotherapy were comparable to that of the 12-month adjuvant aromatase inhibitor therapy for early stage breast cancer patients⁵ or the 12-month androgen deprivation therapy for nonmetastatic prostate cancer patients⁶.
- ✓ We conducted this study to evaluate the efficacy and safety of denosumab for prevention of chemotherapy-induced BMD decreasing.

Patients and Methods

- ✓ This is a multicenter single-arm prospective study to evaluate the efficacy and safety of denosumab in gastrointestinal cancer patients receiving chemotherapy with short-term periodic GC premedication.
- ✓ GIC patients undergoing chemotherapy using periodic GCs administrated as the premedication between Apr 2017 and Feb 2018 were recruited for the study.

Study Objectives

- Primary endpoint:**
BMD variation in the lumbar spine (L2-L4) measured by dual-energy X-ray absorptiometry (DXA) between baseline and 16 weeks after induction of chemotherapy.
- Secondary endpoints:**
- Percent changes in bone turnover marker levels (sBAP and sNTX) between baseline and 16 weeks after induction of chemotherapy.
 - Subgroup analysis of the difference of ECOG PS, sex, primary site, treatment regimen, duration, total cumulative steroid dose, and dose intensity of steroids
 - Safety; low blood calcium and osteonecrosis of the jaw (ONJ)
 - Newly bone fractures, newly bone metastasis
 - JOQOL (Japanese Osteoporosis Quality of Life Questionnaire, 2000 edition)
 - FRAX® output.

Key inclusion criteria

- 1) Diagnosed as histologically confirmed GI malignancies, such as esophageal, gastric, pancreatic, and biliary cancer.
- 2) A schedules of periodical intravenous steroid administration as premedication for prevention of chemotherapy-induced nausea and vomiting or allergic reaction that was weekly, biweekly, and triweekly, and in which >4-week steroid-free intervals were not allowed.
- 3) Age: 40 - 90
- 4) Clinical risk factor score in the JSBMR guideline ≥3.

Key exclusion criteria

- 1) Current regular use of steroids.
- 2) Current regular use of bisphosphonates or other drugs that affect the skeleton.
- 3) Regimens with steroid free interval >4 weeks.
- 4) Patient who cannot do the examination for DXA.
- 5) Past total or partial gastrectomy.
- 6) Except for premenopausal women
- 7) Serum calcium levels <8.0 mg/dL
- 8) On going dental interventional treatment.

Figure 2. CONSORT diagram

Risk factors		Score
Prior fragility fractures	No	0
	Yes	7
Age (years)	< 50	0
	50 ≤ < 65	2
	≥ 65	4
GC dose (PSL equivalent mg/day)	< 5	0
	5 ≤ < 7.5	1
	≥ 7.5	4
Lumbar BMD (%YAM)	≥ 80	0
	70 ≤ < 80	2
	< 70	4

Scoring method in the JSBMR guideline (2015 updated)⁷
JSBMR, Japanese Society for Bone and Mineral Research;
PSL, prednisolone; YAM, young adult mean

Figure 3. Study Schema (ESPRESSO-02)

Planned Sample Size:

45 subjects
In our previous study ESPRESSO-01, the average amount of BMD reduction rate was -1.89%⁴. Assuming that the lower limit of 95% CI of BMD variation rate in this ESPRESSO-02 study will exceed -1.89%, a required sample size was estimated as 36, with a two-sided alpha value of 0.05 and a power of 90%. We estimated that 45 cases would be needed to achieve required cases during patient accrual (2 years) and follow-up periods (a half year) and assuming 20% attrition.

Table 1. Patients Characteristics

Characteristic		n = 42	Characteristic		n = 42
Median age, years (range)	68	(50-81)	Treatment Duration (%)		
Male/Female, n(%)	18/24	(42.9/57.1)	Weekly	10	(23.8)
Primary site (%)			Biweekly	10	(23.8)
Gastric cancer	6	(14.3)	Triweekly	22	(52.4)
Colorectal cancer	24	(57.1)	Treatment Setting (%)		
Pancreas cancer	7	(16.7)	Adjuvant setting	14	(33.3)
Bile duct cancer	5	(11.9)	Non-adjuvant setting (including one neoAdj)	28	(66.7)
Treatment Regimen (%)			Additive Oral steroid usage (%)		
FOLFOX + Pmab	4	(9.5)	Present	14	(33.3)
FOLFOXIRI + Bmab	2	(4.8)	Absent	28	(66.7)
FOLFIRINOX	2	(4.8)	Mean cumulative dose of GCs (range)	87.2 mg	(9.9 – 272.2)
CapeOX ± Bmab	17	(40.5)	Average Dose Intensity* of GCs (range)	5.5 mg/week	(0.6 – 17.0)
Gem + nabPTX	4	(9.5)			
Gem + CDDP	6	(14.3)			
SOX ± Tmab	4	(9.5)			
Iri + CDDP	1	(2.4)			
IRIS + Bmab	1	(2.4)			
DTX + CDDP + S-I	1	(2.4)			

Results

Figure 4. Percent Change in BMD of Lumbar spine + 2.77 % / 16w

Table 2. Percent Change in BMD and

variables	Baseline mean (95% CI)	16 weeks mean (95% CI)	Percent Change mean % (95% CI)	P value*
BMD (g/cm²)				
Lumbar spine	0.92 (0.87 to 0.98) n = 42	0.95 (0.89 to 1.01) n = 42	+ 2.77 (1.35 to 4.20) n = 42	<0.0001
Total hip	0.75 (0.71 to 0.90) n = 41	0.76 (0.72 to 0.80) n = 42	+ 1.36 (0.53 to 2.19) n = 41	0.004
Femoral neck	0.64 (0.60 to 0.67) n = 41	0.65 (0.61 to 0.68) n = 42	+ 1.95 (0.38 to 3.52) n = 41	0.022
Serum BAP (ug/L)	15.53 (12.83 to 18.22) n = 42	9.82 (8.86 to 10.78) n = 42	- 29.44 (-36.41 to -22.48) n = 42	<0.0001
Serum NTX (nmolBCE/L)	23.64 (11.77 to 35.50) n = 30	10.78 (9.13 to 12.42) n = 30	- 37.95 (-48.96 to -26.93) n = 30	0.034

In 30 patients (71.4 % of FAS), the levels of BMD at 16w were increased compared with baseline and the average amount of BMD elevation rate was +2.8 %.

Table 2. Associations of BMD change with variables.

variables	n=42	BMD(LS) change		P value
		Increase	Decrease	
age, years				
≥70	19	15	4	0.49†
<70	23	15	8	
Gender, n(%)				
Male	18	13	5	0.92
Female	24	17	7	
Primary site (%)				
Gastric cancer	6	6	0	0.32†
Colorectal cancer	24	16	8	
Pancreas cancer	7	4	3	
Bile duct cancer	5	4	1	
Treatment Duration (%)				
Weekly	10	8	2	0.27†
Biweekly	10	5	5	
Triweekly	22	17	5	
Treatment Setting (%)				
Adjuvant setting	14	9	5	0.47
Non-adjuvant setting	28	21	7	
Additive Oral steroid usage (%)				
Present	14	10	4	1†
Absent	28	20	8	
baseline T-score‡				
> -2.5	29	22	7	0.34
≤ -2.5	13	8	5	

Conclusions

- ✓ We found that denosumab administration could prevent the secondary reduction of BMD. The lower limit of 95% CI of BMD variation rate in this study was +1.350% and the primary endpoint was met.
- ✓ There was a significant decrease of sBAP and sNTX level statistically.
- ✓ There were no fracture cases in ESPRESSO-02 group.
- ✓ Further study are needed to evaluate on the effectiveness of long-term prognosis, QOL, and cost.

P value data are results of the chi-square test.
† Fisher's exact test
‡ T-score data are represented as any lowest one of the testing lesion, spine, hip, and femoral neck.

References

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