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A Novel Radiosensitizer KORTUC Enhanced Brachytherapy for Unresectable Recurrent Uterine Cervical Cancer

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Introduction

Hypoxia and simultaneous activation of antioxidative enzymes are well known cause of tumor radio-resistance.

A novel radiosensitizer, KORTUC (Kochi Oxydol Radiation Therapy for Unresectable Carcinoma) consists of **hydrogen peroxide (H_2O_2)** as the active ingredient and 1% sodium hyaluronate as excipient to increase H_2O_2 viscosity to sustain the H_2O_2 in the tumor as well as to delay decomposition of H_2O_2 and maintain a high concentration of oxygen.

H_2O_2 is the only agent known to be capable of inactivating antioxidative enzymes and producing oxygen simultaneously to overcome hypoxia-induced radio-resistance (Figure 1).

KORTUC is currently being developed in locally advanced / recurrent breast cancer. Phase 2 clinical trial is being conducted in the UK and India (NCT03946202).

In cervical cancer, tumor hypoxia is also thought to lead to poor treatment outcomes (Lyng and Malinen, 2017).

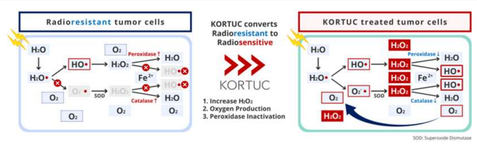

Figure 1. KORTUC Mechanism of Action

Aim and Method

To evaluate the safety and efficacy of KORTUC Intra-tumoral injection in combination with brachytherapy in patients with unresectable recurrent cervical cancer.

We enrolled patients with recurrent cervical cancer who were going to receive interstitial brachytherapy (ISBT) with/without External beam radiotherapy (EBRT) .

For EBRT, KORTUC was injected intratumorally under direct vision of colposcopy or transrectal ultrasound (TRUS) guide within two hours prior to EBRT. For ISBT, KORTUC was administered just after the interstitial applicator placement. If the ISBT was performed for >= 3 consecutive days, KORTUC was additionally injected on third day of the ISBT. The dose of KORTUC ranged from 4 to 12 mL adjusted by tumor size.

(Cont.)

Applicator implantation was performed under TRUS guidance. Ambulatory implantation technique was used. Flexible needle applicators were cut down shortly in order to stand up and walk during treatment. 3D-image CT-based treatment planning with MRI assistance was performed.

Radiation protocol:

- Patients with no previous irradiation history: ISBT combined with EBRT, 24 or 25 Gy in 4 or 5 fractions.
- Patients with previous irradiation history: ISBT as monotherapy, 45.5 Gy in 7 fractions.
- Palliative brachytherapy: Weekly based, the prescribed doses vary depends on each case.

Local response was assessed by CT/MRI or gynecological examination.

Applicators were implanted under TRUS guidance. After implantation, KORTUC was injected.

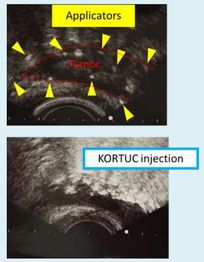

Figure 2. Case presentation: Treatment Protocol of Patient #10

Results

From April 2012 to January 2020, 14 female patients (Age 34-80 yrs old, FIGO IIB to IVB) with 15 lesions of recurrent cervical cancer received KORTUC with brachytherapy. One patient developed recurrence after KORTUC administration and re-enrolled to receive KORTUC at the new site of the lesion. Previous treatments of the patients consisted surgery (n=4), radiation therapy (n=8), and surgery + radiation therapy (n=3) (Table 1).

Table 1. Baseline Demographics and Disease Characteristics

		n (%)
Age	Mean (Min – Max)	55 (34 – 80)
Histology (%)	Squamous cell carcinoma	11 (73.3%)
	Adenocarcinoma	4 (26.7%)
FIGO Stage (%)	IIB	2 (13.3%)
	IIIA	2 (13.3%)
	IIIB	9 (60.0%)
	IVA	2 (13.3%)
	IVB	2 (13.3%)
Prior Therapy (%)	RT	8 (53.3%)
	Surgery	4 (26.7%)
	Surgery + RT	3 (20.0%)

The target lesions of them were vaginal stump (n=5), pelvic wall (n=3), cervix (n=3), vaginal wall (n=2), and lymph node (n=2). 4 out of 15 target lesions received EBRT prior to BT. Median total BED (EBRT+ISBT) was 75 Gy (Table 2).

Patients were followed up for 6 to 116 months (median 24 months). Intratumoral injection of KORTUC was completed as scheduled without any technical or safety issue in any patient. KORTUC injection was well tolerated and no adverse events (AEs) judged to be related to KORTUC were observed, except the transient local pain at the injection site in some patients.

Of 15 patients, 8 patients died from 8 months to 30 months after treatment. Five (33%) had recurrent disease after treatment. Complete response was observed in 86.7% (13/15) and overall response rate (partial response + complete response) was 100.0% (15/15). The 2-year local control rate in patients who received only BT + KORTUC was 55%.

Table 2. Radiation Therapy

Patient ID.	Target lesion	Post surgery	Re-RT	EBRT (Gy x Fr.)	BT (Gy x Fr.)	BED (α/β10)
1	vaginal stump	○		2 x 25	6 x 4	98
2	vaginal stump		○	ND	6.5 x 7	75
3	pelvic wall	○		2 x 25	5 x 5	98
4	LN	○		2 x 25	5x1+8x2	97
5*	vaginal stump	○	○	ND	6.5 x 7	75
6	cervix		○	ND	6.5 x 7	75
7	LN	○		2 x 25	6 x 3	89
8	pelvic wall		○	ND	6.5 x 7	75
9	vaginal wall		○	ND	6.5 x 5	54
10	cervix		○	ND	6.5 x 7	75
11	vaginal wall		○	ND	8 x 5	72
12	pelvic wall		○	ND	12.5 x 2	56
13*	vaginal stump	○	○	ND	6.5 x 7	75
14	vaginal stump	○	○	ND	6.5 x 7	75
15	cervix		○	ND	6.5 x 7	75

*: Same patient, ND; Not Done

Table 3. Patient Outcome

Patient ID.	Initial response	Duration of response after BT (Months)	Recurrence	Follow-up Period (Months)
1	CR	2	No	116
2	CR	2	No	11
3	CR	2	No	61
4	CR	2	No	59
5*	CR	3	Yes	53
6	PR	5	Yes	9
7	CR	7	No	42
8	CR	8	Yes	24 (DT)
9	CR	1	Yes	30 (DT)
10	CR	4	No	6
11	PR	3	No	8
12	CR	6	No	8 (DT)
13*	CR	4	No	32
14	CR	3	No	8
15	CR	6	No	6

*: Same patient, CR: complete response, PR: partial response, DT: dead by tumor

Case Report (Patient #3)

A 63-yr-old female patient had a pelvic sidewall recurrence of uterine cervical cancer. The tumor volume was 89.7 cc. Whole pelvic irradiation of 50 Gy in 25 fractions was administered, combined with weekly cisplatin injections. KORTUC was injected at Day 21 and at Day 24 (the 5th week of EBRT). After finishing EBRT, HDR-ISBT of 25 Gy in 5 fractions b.i.d. over 3 days was administered. KORTUC was also injected after applicator implantation.

The patient showed very good clinical response in the follow up. The MRI at 7-month post-treatment showed a complete radiological response according to RECIST criteria.

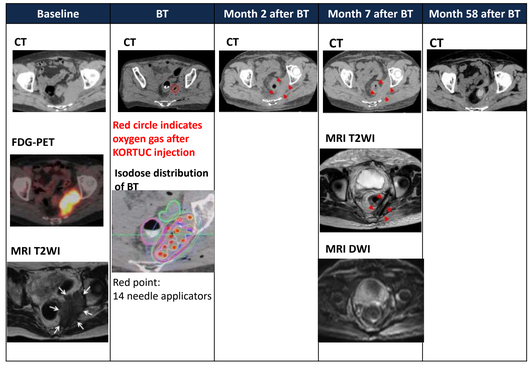

Figure 3. Case presentation: Tumor Response by Imaging in Patient #3

No acute adverse events ≥ grade 3 were observed. Patient experienced grade 3 pyelonephritis as a late toxicity, which was resolved with antibiotics, and other grade 2 late toxicities including sciatic neuralgia, lower limb lymphedema, and urinary incontinence. There was no KORTUC-related adverse events.

Currently, 61 months post-treatment, the patient remains free of disease progression.

Conclusions

This clinical research study suggests that;

- KORTUC intra-tumoral injection is safe and well-tolerated.
- KORTUC is effective for the brachytherapy-sensitizing treatment of recurrent cervical cancer.

To further evaluate KORTUC's effect, a Phase 1/2 clinical trial in locally advanced cervical cancer is planning to start in the US and other countries in 2022. In this planned study, KORTUC will be dosed with EBRT.

References

Ogawa 2016: Ogawa Y, Cancers (Basel). 2016 Feb 25;8(3):28.

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