Proposing Response Evaluation Criteria in Solid Tumors Based on Genomic Profiling or Genomic RECIST: A Retrospective Study on the Liquid Biopsy Results of 29 Cancer Patients

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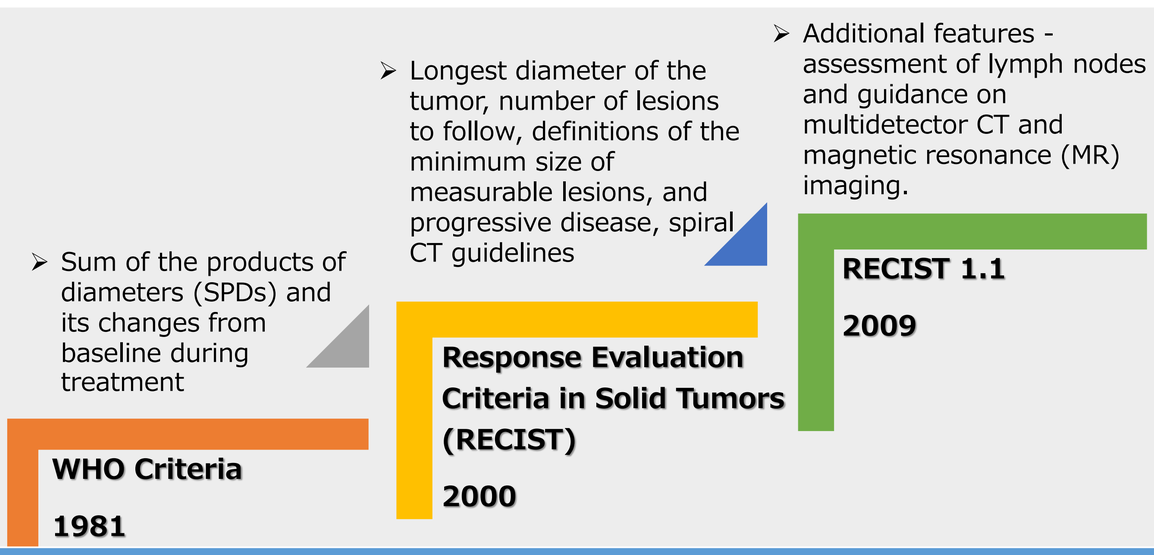
Introduction

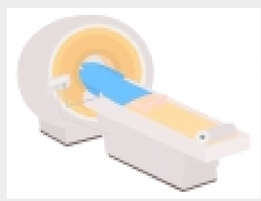
Assessment of Tumor Burden

- Overall survival is the most preferable end of therapeutic efficacy in cancer research.
- However, the tumor response to treatment and time to disease progression can also evaluate the effectiveness of certain cancer treatments.
- The first standardized assessment tool was developed by the World Health Organization (WHO) in 1981.
- To address some pitfalls in WHO criteria, simple and standardized guidelines for the evaluation of therapeutic efficacy were developed in 2000 and called Response Evaluation Criteria in Solid Tumors (RECIST), which was again revised in 2009 with additional features for assessment.
- Using radiological technologies, anatomical size and changes were categorized into four - (a) complete response, (b) partial response, (c) stable disease, and (d) progressive disease.



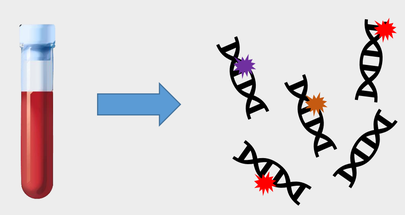
Rationale

Imaging technologies for assessing tumor burden



- Assess gross tumor shrinkage only, no other responses
- Evaluate efficacy of cytotoxic drug
- Takes time to evaluate

Circulating tumor DNA (ctDNA)



- Detects molecular level changes and clonal evolution
- Evaluates efficacy of more advanced, targeted and personalized treatment methods (molecular-targeted therapies, locoregional therapies or immunotherapies, etc.)
- Enables timely and continuous monitoring for prompt actions to be taken

Objectives

1. To examine the quantity and composition of ctDNA results of 29 cancer patients before and after undergoing dendritic cell (DC) immunotherapy with or without chemotherapy and/or radiotherapy

2. To develop criteria to evaluate the molecular response to treatment based on ctDNA results

Methods

Study population and measures

- Retrospective observational study of genomic profiling results in 29 cancer patients who had undergone dendritic cell immunotherapy at the Department of Advanced Medical Science and Technology, Tokyo Midtown Medical Center.
- Blood specimens for liquid biopsy were taken from the patients immediately before and after completion of one course of DC immunotherapy.
- We used GenoDive (GenoDive Pharma, Atsugi, Kanagawa, Japan) assays for genomic profiling of cancer patients in this study.
- Changes in the quantity and composition of circulating tumor DNA (ctDNA) levels were first compared among patients who had received different treatment regimens while undergoing DC immunotherapy.
- These changes were also compared among those diagnosed with different clinical stages after dendritic cell immunotherapy.

Statistical methods

- All continuous variables were expressed as means and standard deviations.
- All categorical variables were expressed as numbers and proportions.
- The calculations and figure generation were performed using Microsoft Excel (Microsoft Corporation, 2018) and R software (R 4.1.0, R Core Team, 2021).

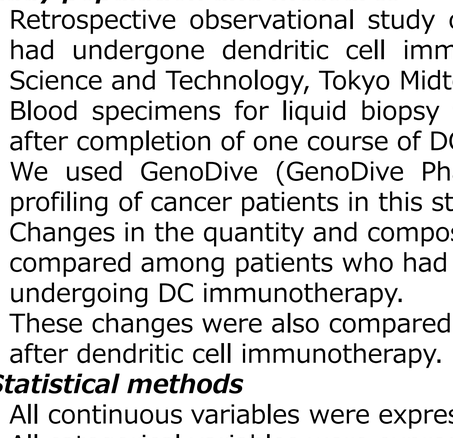
* Calculation: The change in total ctDNA was calculated as the percent of total ctDNA after the treatment (LB2) as the numerator and the percent of total ctDNA at baseline (LB1) as the denominator. The percentage of total ctDNA was the titer of ctDNA divided by that of cell-free DNA (cfDNA). Baseline ctDNA must be at least 0.1% to be eligible for this calculation.

Setting genomic RECIST with reference to RECIST 1.1

RECIST 1.1	Genomic RECIST	Total ctDNA changes* (LB2/LB1 ratio)
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.	gCR	<0.01
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.	gPR	0.01-0.69
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.	gSD	0.7-1.2
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.	gPD	>1.2

Results

Figure 1. Types of cancer in the study cohort



Gastroenterological cancers such as pancreatic, colorectal, stomach, and biliary cancers constituted more than half of the participants.

Figure 2. Comparison of clinical and genomic RECIST

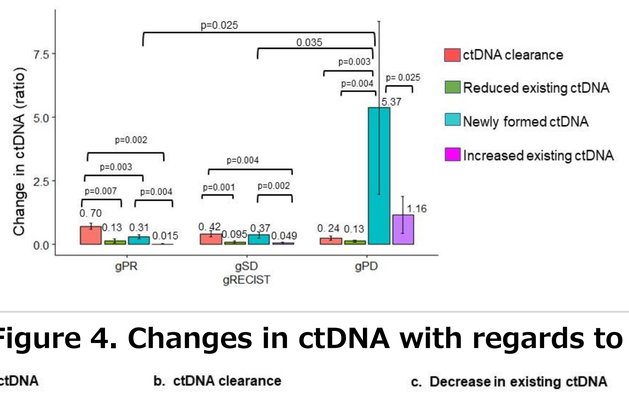
	gCR	gPR	gSD	gPD	RECIST 1.1 total
CR				1	1
PR		1	3	2	6
PR/SD			1	1	2
SD		6	3	7	16
SD/PD				1	1
PD			1	2	3
gRECIST total		7	8	14	29

Even those who are clinically evaluated as having a good response might harbor unfavorable tumor responses at the molecular level.

Figure 3. Clonal evolution results in genomic RECIST

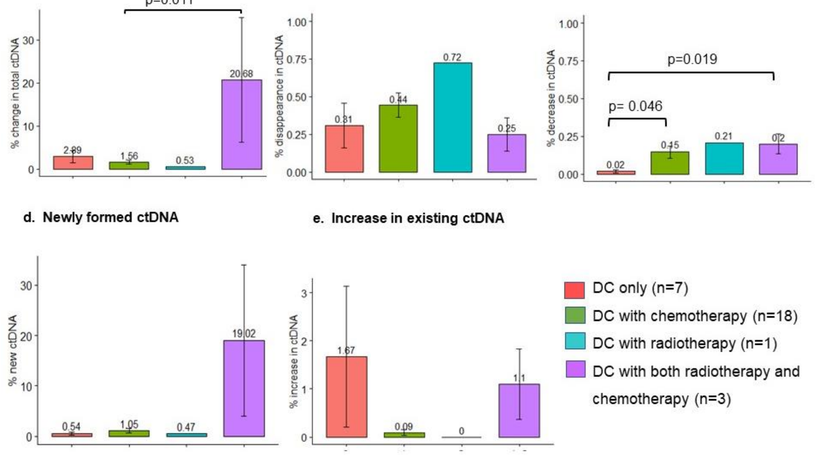
gRECIST	n	Total ctDNA*	ctDNA clearance*	Decrease in existing ctDNA*	Newly formed ctDNA *	Increase in existing ctDNA*
gPR	7	0.47 (0.032~0.65)	0.70 (0.14~1)	0.13 (0~0.57)	0.31 (0.032~0.64)	0.015 (0~0.066)
gSD	8	0.92 (0.76~1.09)	0.42 (0.011~1)	0.095 (0~0.3)	0.37 (0.019~0.93)	0.049 (0~0.34)
gPD	14	7.16 (1.27~49.2)	0.24 (0~0.46)	0.13 (0~0.4)	5.37 (0.094~48.6)	1.16 (0~10.4)

*All are mean ratio values with ranges (shown in brackets),



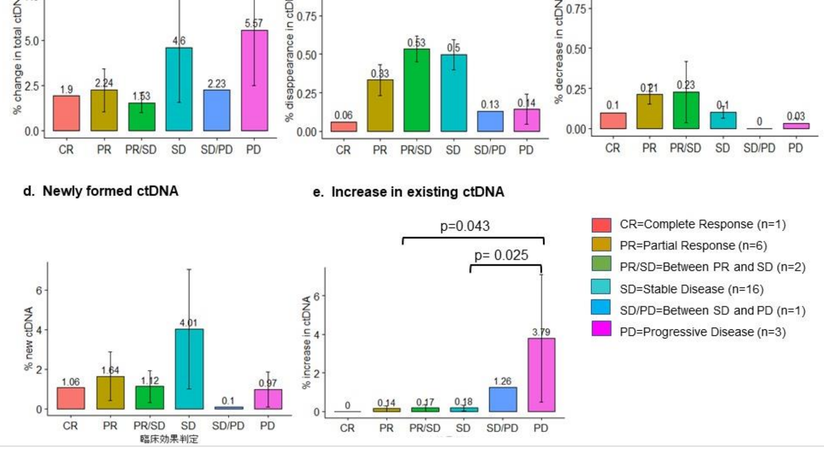
Newly formed ctDNA levels can be the most prognostic parameter in tumor progression or treatment response, while ctDNA clearance and the decline or rise in existing ctDNA did not change significantly in genomic response categories (gRECIST).

Figure 4. Changes in ctDNA with regards to treatment regimens



The patients who received both chemotherapy and radiotherapy during DC immunotherapy had the highest percent changes in total ctDNA and newly formed ctDNA. Patients who underwent DC immunotherapy alone had the least decrease in ctDNA.

Figure 4. Changes in ctDNA with regards to clinical response



Even in clinically stable cases, there could be high ctDNA due to newly formed ctDNA. A significantly increasing trend in existing ctDNA was observed as the diseases progressed clinically.

Discussions and conclusions

Discussions

- Not only ctDNA clearance but also **newly formed ctDNA** levels can be prognostic in tumor progression or treatment response.
- In gPR category, approximately 30% of newly formed ctDNA was noted, reflecting the **dynamic state of tumor evolution**.
- Those clinically evaluated as **good response might have unfavorable molecular response**. For example, even in clinically stable cases, ctDNA can be high because of newly formed ctDNA, although the existing ctDNA level decreases.
- **Close monitoring of ctDNA titer and composition** can assess more precise tumor response.
- Hence, monitoring ctDNA is **critical in cancer prognosis** and should be incorporated in the **clinical monitoring of cancer patients**.

Conclusions

- This is the first and only to propose using genomic RECIST and liquid biopsy results in various tumors after DC immunotherapy with standard cancer treatments.
- Our study showed that genomic RECIST could be useful to monitor the treatment response, disease progression, and the selection of potential effective treatment in cancer patients.
- Additionally, our study highlighted that more delicate and precise assessment was feasible by prospectively monitoring ctDNA values.
- Although generalizability remains an issue, these findings have opened up further potential for real-world data and evidence to support the clinical use of ctDNA in precision oncology and personalized cancer treatment.

References: