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Interferon-α-based Immunotherapy in Metastatic Renal Cell Carcinoma Patients with the Primary Tumor *In Situ*

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Objective: We reviewed the outcomes of metastatic renal cell carcinoma patients with the primary tumor *in situ* who initially underwent interferon-α-based immunotherapy to evaluate the effect of this therapy on metastatic sites as well as primary kidney tumor and survival.
Methods: Thirty-one patients, for whom upfront cytoreductive nephrectomy was considered to be inappropriate because of poor performance status and far-advanced disease, were the subject of the present study. Tumor response and reduction in the size of metastatic sites and primary kidney tumor were assessed. Overall survival distributions were estimated using the Kaplan–Meier method with the significance determined using the log-rank test.
Results: Partial response was observed in 11 patients, yielding an overall response rate of 35%. Seventeen patients had regression or stabilization of metastatic sites, while progression of metastatic sites was observed in the remaining 14 patients. Regarding the maximum response of primary kidney tumor, a reduction in kidney primary tumor size was observed in 42% of the patients and the mean reduction rate in these patients was 18.2% (range: 3–36%). Furthermore, the reduction in the size of metastatic sites was significantly associated with that in the size of primary kidney tumor ($R^2 = 0.432$, $P < 0.0001$). The median survival for the 31 patients was 17 months. The median survival was 42 months in patients with regression or stabilization of metastatic sites and 7 months in those without ($P < 0.001$).
Conclusions: The present study suggests that metastatic sites as well as primary kidney tumor respond to interferon-α-based immunotherapy in metastatic renal cell carcinoma patients with primary tumor *in situ*.

Key words: metastatic RCC – primary tumor in situ – IFN-α – metastasis

INTRODUCTION

The prognosis of patients with metastatic renal cell carcinoma (RCC) has been very poor. The median survival of patients with metastasis at initial diagnosis of RCC is reported to be ~12 months (1). For these patients, cytoreductive nephrectomy followed by systemic therapy is, in general, thought to be a feasible treatment strategy (2). However, the survival benefit obtained by cytoreductive nephrectomy was limited to patients with good performance status (PS) and resectable primary tumor. Cytoreductive nephrectomy for patients with poor PS or hardly resectable RCC has been controversial (3). An alternative approach for these patients would be the administration of systemic therapy with the primary kidney tumor *in situ*.

Molecular-targeted drugs that target vascular endothelial growth factor or cell growth pathways have revolutionized the treatment of metastatic RCC with the results of increased survival and improved response rates (4–6). To date, several clinical trials have been conducted to evaluate the feasibility of presurgical molecular-targeted therapy in metastatic RCC patients with primary kidney tumor. On the other hand, cytokine therapy has been widely believed to be less beneficial because cytokine therapy is not effective for patients with primary tumor *in situ* (7). We also performed cytoreductive nephrectomy in almost all patients with metastatic RCC as much as possible. However, rapid exacerbation after surgery occurred in most patients with poor preoperative PS, difficulty in surgery or symptomatic aggressive metastatic disease. In 1995, we changed our treatment approach for the patients for whom upfront cytoreductive nephrectomy was considered to be inappropriate as follows: interferon (IFN)-α-based immunotherapy is administered beforehand in patients with primary kidney tumor *in situ*, and subsequent cytoreductive nephrectomy is performed only when the metastatic lesion can be controlled. We retrospectively reviewed the outcomes of these patients to evaluate the effect of IFN-α-based immunotherapy on metastatic sites as well as primary kidney tumor and on survival.

PATIENTS AND METHODS

Patients

From 1995 until 2007 (so-called the cytokine era in Japan), 138 RCC patients with metastases at initial visit were treated at our department and three affiliated hospitals. Of these, 31 patients, for whom upfront cytoreductive nephrectomy was considered to be inappropriate because of poor PS or far-advanced disease, were the subject of the present study (Table 1). In the present study, poor PS was defined as Eastern Cooperative Oncology Group (ECOG)-PS 2 or more, and far-advanced disease was defined as >T3 N_{any} M1 disease or aggressive metastasis with symptoms. No patients had biopsy confirmation of RCC histology before initiation of IFN-α-based immunotherapy and received any therapy including previous immunotherapy with IFN-α or interleukin (IL)-2. The evaluable patients with kidney tumor initially received natural IFN-α [3×10^6 international units (IU) Sumiferon per day, Dainippon Sumitomo Pharma, Osaka, Japan, or 5×10^6 IU OIF per day, Otsuka Pharmaceutical, Tokyo, Japan] three times weekly for 6–12 months. Twenty-seven patients received several drugs in combination with IFN-α: meloxicam ($n = 17$), cimetidine ($n = 7$), dexamethasone ($n = 6$) or IL-2 ($n = 1$). Tumor responses of metastatic sites were assessed by standard imaging modalities every 3 months. Cytoreductive nephrectomy was recommended for the patients in whom regression or stabilization in the size of metastatic sites was achieved 6 months after initiation of IFN-α-based immunotherapy. The timing of cytoreductive nephrectomy in these patients was finally decided on the basis of the general health condition or wishes of the patient, and IFN-α-based immunotherapy was continued by the time of cytoreductive nephrectomy. On the other hand, the patients with progression of metastatic sites did not undergo cytoreductive nephrectomy.

Clinical, pathological and survival data were collected for each patient. The stage was assigned according to the 1997 TNM classification of the Union Internationale Contre le Cancer (UICC). Laboratory data included hemoglobin, serum lactate dehydrogenase (LDH), corrected Ca (cCa) and C-reactive protein (CRP). LDH values were standardized against the upper limit of normal (ULN) in each participating hospital when appropriate. The cCa was

Table 1. Patient characteristics

Median age (range)	64 (37–87)
Sex (%)	
Male	21 (68%)
Female	10 (32%)
ECOG-PS (%)	
0	4 (13%)
1	8 (26%)
2	17 (55%)
3	2 (6%)
MSKCC risk classification (%)	
Intermediate	6 (19%)
High	22 (71%)
Not evaluable	3 (10%)
Median size of primary kidney tumor (range)	8 cm (4–16)
Median FPTV (range)	55% (21–91)
IVC tumor thrombus (%)	16 (52%)
Number of metastatic sites (%)	
1	11 (35%)
2	16 (52%)
>3	4 (13%)
Metastatic sites (%)	
Lung	27 (87%)
Lymph nodes	11 (35%)
Bone	10 (32%)
Liver	4 (13%)
Others	5 (16%)
IFN-α-based treatment (%)	
IFN-α	13 (42%)
IFN-α + molexicam	17 (54%)
IFN-α + IL-2	1 (3%)

ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; MSKCC, Memorial Sloan Kettering Cancer Center; FPTV, fractional percentage of tumor volume; IVC, inferior vena cava; IFN, interferon; IL, interleukin.

calculated employing Orrell's formula (cCa = Ca − 0.707 × [alb-3.4]) (8). The pathological findings were determined according to the General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma in Japan. Fractional percentage of tumor volume (FPTV) was also determined by the diameter of the primary kidney tumor divided by the diameter of the total targeted lesions including primary kidney tumor according to Response Evaluation Criteria in Solid Tumors (RECIST) (9). Prognostic assessment was performed according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification (10). The institutional review board and/or ethical committee at all participating institutions approved the protocol of this study.

Evaluation of Response

Baseline evaluations included physical examination, ECOG-PS, full blood count and serum chemistry analyses as well as tumor assessment. The patients were requested to attend the outpatient clinic every 4 weeks for a physical examination, biochemistry tests and assessment of adverse events. Treatment efficacy was assessed every 3 months with chest and abdominal computed tomography scans. Tumor response and reduction rate in tumor size of metastatic sites and primary kidney tumor were assessed according to RECIST at 6 months after initiation of IFN-α-based immunotherapy. Magnetic resonance imaging and bone scintigraphy were performed at baseline to screen for brain and bone metastases, respectively, and were repeated when any relevant symptom developed after the start of treatment.

Statistical Methods

Patient characteristics are shown as median for continuous variables and number of patients with percentage for categorical variables. Differences across the groups divided according to the response of metastatic sites regarding all categorical variables were examined with χ^2-test. For continuous variables, the Mann–Whitney *U*-test was used. The correlations between reduction rate in the size of metastatic sites and that in primary kidney tumor size were assessed by linear regression analysis. Overall survival (OS) was calculated from the date of the initiation of IFN-α-based immunotherapy to the date of death as a result of any cause or was censored at the date of the last follow-up. Survival distributions were estimated using the Kaplan–Meier method with the significance determined using the log-rank test. The median OS along with the 95% confidence interval (95% CI) was reported. For all statistical analyses, P values <0.05 were considered significant. All statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC, USA).

RESULTS

The distribution of baseline characteristics for the 31 patients with the primary tumor *in situ* is presented in Table 1. Of these, eight patients were subjects who were evaluated in a previous study (11). According to the MSKCC risk classification, 6 patients were classified as at intermediate risk and 22 patients as at poor risk. The median kidney primary tumor size was 8 cm (95% CI, 7.8–10.1 cm) and the median FPTV was 55% (95% CI, 49–62%). Nine patients (29%) had pulmonary metastasis alone. In combination with IFN-α-based immunotherapy, radiotherapy was performed in nine patients with bone metastasis ($n = 7$) or brain metastasis ($n = 3$). Furthermore, three patients with bone metastasis received zoledronic acid. The median follow-up was 17 months (range: 3–110+ months).

In terms of objective response of all evaluable lesions, partial response (PR) was observed in 11 of the 31 patients, yielding an overall response rate of 35%. Seventeen patients had regression or stabilization in the size of metastatic sites (response group), while progression of metastatic sites was observed in the remaining 14 patients (non-response group). Comparison of pretreatment variables between the response group and the non-response group is shown in Table 2. There was a significant difference in pretreatment PS between these two groups. Thirteen (76%) of the 17 patients who received IFN-α combined with meloxicam had response of metastatic sites, while this was the case for only 4 (28%) of the 14 patients who did not receive meloxicam. Of the 17 patients with regression or stabilization of metastatic sites by the IFN-α-based immunotherapy, 13 patients underwent cytoreductive nephrectomy 6–18 months (median 9 months) after the initiation of IFN-α-based immunotherapy. Pathological examination of primary kidney tumor showed that viable cancer persisted in all patients (clear cell carcinoma in 11 patients, chromophobe RCC in 1 and type 1 papillary RCC in 1).

Regarding the maximum response of primary kidney tumor, reduction in kidney primary tumor size was observed in 13 (42%) of 31 patients, and the mean reduction rate in these patients was 18.2% (range: 3–36) (Fig. 1). While 4 (13%) of the 31 patients had >30% decrease in primary tumor size, 7 (23%) patients had >20% increase. Furthermore, the reduction rate in the size of metastatic sites was revealed to be significantly associated with that in the size of primary kidney tumor in linear regression analysis ($R^2 = 0.439$, $P < 0.0001$) (Fig. 1). Figure 2 shows a representative patient with lung metastasis. By administering IFN-α and meloxicam for 11 months, lung metastasis completely disappeared and significant reduction in primary kidney tumor size was observed.

The median OS for the 31 patients was 17 months. When OS was compared with the response of metastatic sites to IFN-α-based immunotherapy (Fig. 3), the median OS was 42 months in the response group and 7 months in the non-response group ($P < 0.001$). In the response group, the

Table 2. Patient distribution in terms of response of metastatic sites to IFN-α-based therapy

Variables	Response group ($n = 17$)	Non-response group ($n = 14$)	P value
Median age	64	63.5	0.921
Sex: male (%)	13 (76%)	8 (57%)	0.447
Tumor side: right (%)	10 (59%)	10 (71%)	0.724
T-stage: ≥T3	15 (88%)	9 (64%)	0.248
ECOG-PS >2 (%)	7 (41%)	12 (86%)	0.031
Median tumor size (cm)	8.0	9.0	0.921
Median FPTV (%)	55	53	0.462
IVC thrombus (+)	10 (59%)	6 (43%)	0.600
Number of metastases			
Multiple (%)	10 (59%)	10 (71%)	0.724
Metastatic sites			
Extrapulmonary (%)	10 (59%)	12 (86%)	0.214
Pretreatment blood chemistry[a]			
Anemia[b] (%)	12 (80%)	12 (92%)	0.699
Median WBC	6100	6000	0.533
Median platelet ($\times 10^4$)	26.8	26.8	0.890
LDH > 1.5× ULN (%)	2 (13%)	3(23%)	0.860
Median cCa (IU/l)	9.5	9.6	0.282
Median CRP (mg/dl)	2.89	4.29	0.182
MSKCC risk classification:			
Poor risk (%)	11 (71%)	11 (85%)	0.792

WBC, white blood cells; LDH, lactate dehydrogenase ULN, upper limit of normal; cCa, corrected Ca; CRP, C-reactive protein.
[a]Because of missing data, the number of patients evaluable was 15 in the response group and 13 in the non-response group.
[b]Anemia: <13.5 (male)/<11.5 (female).

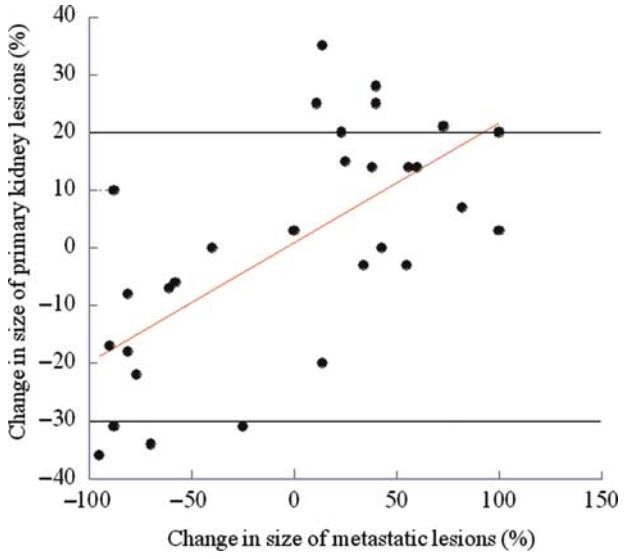

Figure 1. The relationship between the change in size of metastatic lesions and that of primary kidney tumor. Bold lines indicate partial response and progressive disease, as defined by RECIST.

2-year OS was significantly higher in patients who underwent cytoreductive nephrectomy than in those who did not [92.3% (95% CI, 77.8–100) vs. 25% (95% CI, 0–67), $P < 0.001$].

DISCUSSION

The present study demonstrated that IFN-α-based immunotherapy might be effective even in metastatic RCC patients with the primary tumor *in situ*, especially with ECOG-PS 0 or 1. The effects of IFN-α-based immunotherapy were observed in not only distant metastatic sites but also the primary tumor itself. The survival time was significantly longer in patients with regression or stabilization of distant metastatic sites than in those without.

It is generally recommended that cytoreductive nephrectomy be performed in RCC patients with metastasis on initial examination, followed by immunotherapy with IFN-α or IL-2, on the basis of two randomized trials (SWOG 8949 and EORTC 30957) performed by Flanigan et al. (12) and Mickisch et al. (13). Most clinicians believed that cytoreductive nephrectomy should be performed as much as possible when IFN-α is administered. On the other hand, the response rates of metastatic lesions were 3.6% in the patients treated with cytoreductive nephrectomy followed by IFN-α treatment and 3.3% in the patients treated with IFN-α monotherapy in the SWOG 8949 trial (12) and 19 and 12% in the EORTC 30597 trial (13), respectively. These results suggest that the survival time may differ with the presence or absence of cytoreductive nephrectomy, but treatment effects of IFN-α treatment on distant metastases may be similar.

Is it then clinically meaningful to perform cytokine therapy followed by cytoreductive nephrectomy? Wagner et al. (7) performed high-dose IL-2-based therapy in metastatic RCC patients with the primary tumor *in situ*. They observed that IL-2-based therapy had a therapeutic effect on metastatic lesions in only 3 of the 51 patients; cytoreductive nephrectomy was applicable in only 3 patients and the duration of response was unsatisfactory (4, 11 and 88 months, respectively). On the basis of these findings, cytokine therapy in the presence of the primary renal lesion is considered to be less beneficial in North America and Europe. In Japan, no such clinical study has been performed, but many physicians have the same impression from their clinical experience. In the present study, regression or stabilization of distant metastatic sites was noted in 55% of patients, contrary to the commonly held view that IFN-α-based therapy is ineffective in metastatic RCC patients with the primary tumor *in situ*. The effective patients had good PS (PS 0 or 1) and were mostly treated with IFN-α and meloxicam combination therapy. Meloxicam is a Cox-2 inhibitor, and we reported that meloxicam potentiated the effect of IFN-α (11). Yoshino and Okabe (14) also reported a case of notable tumor shrinkage caused by the combination of natural IFN-α and meloxicam. Furthermore, DeLong et al.

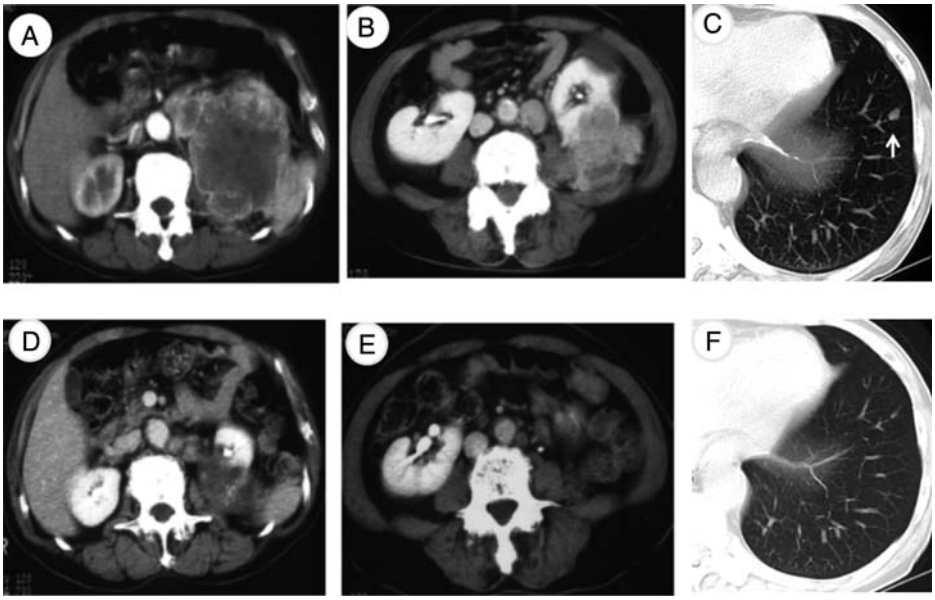

Figure 2. By administering interferon-α and meloxicam for 11 months, significant reduction in primary kidney tumor was observed and small lung metastasis disappeared. (A–C) Pre-treatment image of primary kidney tumor (11 cm in diameter) and lung metastasis (arrow) (D–F) post-treatment image of primary kidney tumor (7 cm in diameter; reduction rate 36%).

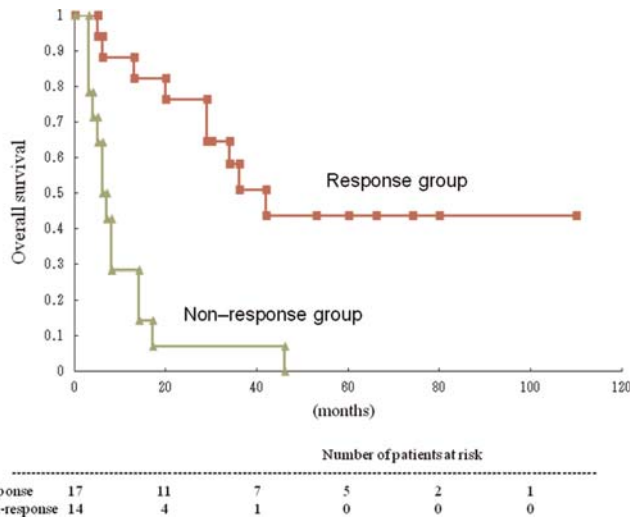

Figure 3. The Kaplan–Meier curves of overall survival for patients belonging to the response group ($n = 17$) and for those belonging to the non-response group ($n = 14$). The prognosis of patients in the non-response group was significantly worse than that of those in the response group ($P < 0.0001$).

(15) studied a lung cancer cell line and found that the effect of IFN-α gene therapy was enhanced by the COX-2 inhibitor and that proliferation of transplanted mouse tumors was strongly suppressed.

We previously considered that this effect was limited to metastatic sites and does not markedly influence the primary kidney tumor. However, the present study demonstrated that a reduction in primary tumor size occurred in 42% of patients and the mean reduction rate of these patients was 18%. Furthermore, the reduction rate in primary kidney tumor size was significantly associated with the reduction rate in the size of metastatic sites. These results suggest that there are therapeutic effects of IFN-α-based immunotherapy on the primary kidney tumor as well as metastatic sites. Abel et al. (16) reported similar results in patients who underwent presurgical therapy with targeted agents. In their retrospective study, 59% of evaluated patients had PR or stable disease (SD) in metastatic disease sites during treatment; in addition, primary tumor response >10% was associated with PR or SD in metastatic sites.

Is the effect of cytokine therapy in metastatic RCC patients with the primary tumor *in situ* limited to our patients? In the Global ARCC trial in which the therapeutic effects of IFN-α and temsirolimus were compared, stratified analysis was performed in patients without resection of the primary renal lesion (17). Although size reduction in the primary lesion was observed in about 60% of cases treated with temsirolimus, size reduction in the primary lesion was also observed in ~30% of cases treated with IFN-α. This is surprising because most patients involved in this trial were classified into the high-risk group. Donskov et al. (18) performed IL-2-based therapy for patients with both primary and metastatic renal cancers and then nephrectomy only in cases in which an effect on distant metastatic lesions was observed, similarly to our study; not only the distant metastatic lesion but also the primary lesion shrank, although the number of patients was small. Bex et al. (19) first performed cytokine therapy in a group with intermediate risk according to the MSKCC risk classification, and then applied cytoreductive nephrectomy only to patients in whom distant metastatic lesions were controlled. Distant metastasis became

progressive disease in 10 of the 31 patients (30%) and cytoreductive nephrectomy was not performed, whereas it became PR and SD in 21 patients (70%) and cytoreductive nephrectomy was performed. No primary lesion grew during cytokine therapy and made cytoreductive nephrectomy non-applicable in any of these patients. Although the number of reports is small, these studies suggest that cytokine therapy is effective in metastatic RCC patients with the primary tumor *in situ*.

We also investigated whether control of the metastatic lesion influenced the survival time. In the present study, the survival time was 46 months in patients in whom distant metastasis was controlled by IFN-α-based therapy but only 7 months in those in whom distant metastasis could not be controlled. The effect of cytoreductive nephrectomy may have been enhanced in patients in whom distant metastasis was controlled and the surgery was subsequently performed. Similarly, the median survival time was 17 months in patients who underwent cytoreductive nephrectomy following control of distant metastatic lesions in the above study reported by Bex et al. (19), showing apparent prolongation of the survival time compared with that of 10 patients without the surgery.

Lastly, we should emphasize that the present study has several limitations, including its retrospective nature that are associated with selection bias and the small number of patients evaluated. The potential selection bias appears to occur when we judged whether IFN-α-based immunotherapy was administered beforehand and whether the patient should undergo cytoreductive nephrectomy. Although there are many problems to be solved in the present study, the outcomes do suggest that combined treatment with IFN-α-based immunotherapy, especially with IFN-α/meloxicam combination therapy, and subsequent cytoreductive nephrectomy can be successful in selected patients with poor prognostic features.

The present study suggests that metastatic as well as primary lesions respond to IFN-α-based therapy in metastatic RCC patients with the primary tumor *in situ*. In addition, subsequent cytoreductive nephrectomy following such responses of distant metastatic lesions may lead to prolongation of the survival time. The outcome obtained from the present study could indicate the possibility of presurgical therapy with IFN-α-based therapy in metastatic RCC patients. We now recommend this treatment approach to the patients with good PS who have locally advanced disease (more than T3) and lung metastases alone. Since Ito et al. (20) recently demonstrated that the single-nucleotide polymorphisms in signal transducer and activator 3 (STAT3) gene were associated with sensitivity to IFN-α, an analysis of STAT3 polymorphism would offer more valuable information to select suitable patients regarding presurgical therapy with IFN-α-based therapy in metastatic RCC patients. Further clinical studies involving a large number of patients are required.

Conflict of interest statement

Nobuo Shinohara has received speaker honoraria from Novartis and Pfizer.

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