JBUON 2015; 20(2): 580-587
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Does neoadjuvant chemotherapy plus cytoreductive surgery improve survival rates in patients with advanced epithelial ovarian cancer compared with cytoreductive surgery alone?

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Summary

Purpose: *To compare the outcomes of interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC/IDS) with primary debulking surgery (PDS) in patients diagnosed with advanced epithelial ovarian cancer (EOC).*

Methods: *A total of 292 patients with stages IIIC and IV disease who were treated with either NAC/IDS or PDS between 1995 and 2012 were retrospectively reviewed. The study population was divided into two groups: the NAC/IDS group (N=84) and the PDS group (N=208). Progression-free survival (PFS), overall survival (OS), and optimal cytoreduction were compared.*

Results: *The mean age was significantly higher in the NAC/IDS group (61.5±11.5 vs 57.8±11.1 years, p=0.01). Optimal cytoreduction was achieved in 34.5% (29/84) of the patients in the NAC/IDS group and in 32.2% (69/208) in the PDS group (p=0.825). The survival rates were comparable. The mean survival rate of patients who achieved optimal cytoreductive surgery in either the PDS or the NAC/IDS arm was significantly higher than that of patients who achieved suboptimal cytoreductive surgery (p<0.001 and p<0.001, respectively). Multivariate analysis confirmed the treatment method, amount of ascitic fluid, and optimal cytoreduction as independent factors for OS.*

Conclusions: *No definitive evidence was noticed regarding whether NAC/IDS increases survival compared with PDS. NAC should be reserved for patients who cannot tolerate PDS or when optimal cytoreduction is not feasible.*

Key words: *debulking surgery, neoadjuvant chemotherapy, ovarian cancer, primary, survival*

Introduction

EOC is the most common type of ovarian cancer, and the majority of patients are diagnosed at an advanced stage [1]. The current standard treatment for EOC consists of PDS followed by chemotherapy. Some authors [2-5] report a potential benefit from an alternative treatment consisting of interval debulking surgery after neoadjuvant chemotherapy (NAC/IDS) for some patients with advanced-stage disease. However, the results of a large meta-analysis involving 835 patients suggested that NAC/IDS, compared with PDS, was associated with a worse outcome [6].

Optimal cytoreductive surgery is one of the most significant prognostic factors for the survival of patients with advanced EOC [7]. In a study by Romanidis et al. it was concluded that hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) combined with complete cytoreductive surgery was an encouraging treatment approach in women with advanced EOC and recurrent dis-

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Received: 13/08/2014; Accepted: 31/08/2014

ease [8]. However, advanced disease sometimes makes optimal cytoreductive surgery more aggressive and occasionally difficult to accomplish. In these cases, extensive surgical procedures, such as bowel resection, splenectomy, and partial hepatectomy, are often required. Such patients usually have multiple comorbidities and poor nutritional status. Consequently, an aggressive surgical approach is limited in these patients. The goal of NAC is to increase the feasibility of optimal cytoreduction. Thus, NAC/IDS has been considered as an alternative to PDS in the treatment of advanced EOC. According to some studies, patients who were treated with NAC/IDS had comparable survival rates to those who underwent PDS [2,9].

The aim of this study was to compare the outcomes of patients diagnosed with EOC who were treated with NAC/IDS with those who were treated with PDS alone.

Methods

All patients who had undergone surgery for EOC at the Tepecik Training and Research Hospital, Izmir, Turkey, between January 1, 1995, to December 31, 2012, were retrospectively reviewed. A total of 379 patients with International Federation of Gynecology and Obstetrics (FIGO) EOC stage IIIC and IV who were treated with either NAC/IDS or PDS was identified. These patients were divided into two separate groups based on the type of treatment they received. The number of patients who underwent surgery after NAC was 113. Nineteen patients were excluded because of incomplete data. Ten patients who received more or less than 3 or 4 cycles of chemotherapy (standard NAC treatment protocol) were also excluded. Finally, a total of 292 patients who had complete clinical data (84 patients were included in the NAC/IDS group and 208 patients in the PDS group) were analyzed.

The reported reasons for primary therapy with NAC were extra-abdominal disease verified by imaging methods and extensive intra-abdominal disease that was deemed unresectable by the primary surgical team. In addition, NAC was administered when the patients could not tolerate radical surgery due to advanced age, poor general condition, and/or the presence of comorbidities.

Total abdominal hysterectomy with bilateral salpingo-oopherectomy, infra-gastric omentectomy and cytological analysis were performed in all cases. Resection of peritoneal implants by stripping the pelvic, abdominal, and/or diaphragmatic peritoneum were performed in some eligible cases. The decision to perform systematic pelvic and para-aortic lymphadenectomy was determined by the surgical team.Colorectal, small bowel, and upper abdominal organ resections were also performed when necessary. The general goal was to remove as much of the tumor as possible to achieve optimal cytoreduction, which was defined as residual disease ≤1 cm according to the Gynecologic Oncology Group (GOG).

The clinical stage, distribution of serum CA 125 levels, adequacy of surgery, optimal cytoreduction rates, perioperative and postoperative complications, perioperative blood transfusion requirements, duration of hospital stay, and mean survival rates were compared between the two groups. Surgical complications were graded according to a previously published institutional grading system [10]. Grade 1 complications were those that were managed with oral medications; grade 2 complications required intravenous management; grade 3 complications required major organ resection, interventional radiology, and/or re-operation for correction; grade 4 complications were those that resulted in permanent impairment of organs' function; and, finally, grade 5 complications were those that resulted in the death of the patient within 30 days of the primary surgery [11]. PFSwas defined as the time interval from the date of surgery to the date of the first documented recurrence or progression of disease. If there was no recurrence, PFS was determined as the date of the last follow-up or death, whichever occurred first. OS was defined as the time interval between the date of surgery and the date of death or last follow-up visit.

Statistics

Statistical analysis was performed using the IBM SPSS Statistics 21.0 software (SPSS Inc., Chicago, Ill). The variables were assessed using visual (histograms, probability plots) and analytical (Shapiro-Wilk test) methods to determine whether they were normally distributed. Continuous data (presented as the means ± SD) that were normally distributed were analyzed using Student's t-test, while data that were not normally distributed were analyzed using the Mann-Whitney U test. Paired continuous data that were not normally distributed were analyzed using the Wilcoxon signed rank test. The Pearson's exact chi-square or Fisher's exact test were used to compare the proportions between groups. The Kaplan-Meier method were used to generate survival curves, and a comparison was made with the log rank test. Univariate and multivariate logistic regression models were used to identify the risk factors. A p value <0.05 was defined as statistically significant.

Results

In the NAC/IDS group, 83 (98.8%) patients were administered 3 courses of chemotherapy, while 1 patient was administered 4 courses. Seventy patients received paclitaxel/carboplatin and 14 received docetaxel/carboplatin as NAC regimens. Paclitaxel was administered at a dose of 175 mg/m^2 in association with carboplatin at an

Table 1. Baseline characteristics of the patients in the two groups

Characteristics	*NAC/IDS group (N=84) N (%)*	*PDS group (N=208) N (%)*	*p value*
Age, years	61.5 ± 11.5	57.8 ± 11.1	0.01
Presence of comorbidities	61 (71.8)	81 (39.1)	<0.001
Stage			0.38
IIIC	75 (89.3)	191 (91.8)	
IV	9 (10.7)	17 (8.2)	
Histology			0.01
Serous	68 (80.9)	207 (99.5)	
Other	16 (19.1)	1 (0.5)	
Grade			0.84
I	10 (11.9)	21 (10.1)	
II	20 (23.8)	58 (27.9)	
III	53 (63.1)	128 (61.5)	
Unknown	1 (1.2)	1 (0.5)	
Pretreatment serum CA-125 (U/mL)(range)	731 (62-10842)	600 (33-11543)	0.019
Pleural effusion	36 (42.8)	85 (40.9)	0.89

Values for continuous variables are means ± SD or medians [minimum-maximum]. Values for categorical variables are the number/ total number of cases (%). A p value <0.05 was considered to be statistically significant. NAC/IDS : Interval debulking surgery after neoadjuvant chemotherapy, PDS: Primary debulking surgery

area under the curve of 5 or 6 (AUC 5-6). Docetaxel was administered at a dose of 75 mg/m2 in association with carboplatin (AUC 5 or 6). Courses were repeated every 3 weeks. All patients underwent debulking surgery following NAC. To complete the full treatment regimen of 6 cycles, all patients received 2 or 3 cycles postoperatively.

Table 1 shows the baseline characteristics of the 84 patients who were treated with NAC/IDS and the 208 patients who were treated with PDS. The median pre-chemotherapy serum CA-125 level was 731 U/mL (range 62-10842) in the NAC/IDS group and the median pre-operative serum CA-125 level was 600 U/mL (range 33-11543) in the PDS group (p=0.019). The median serum CA-125 level after chemotherapy in the NAC/IDS group was 137 U/mL (range 5-2660), showing statistically significant decrease (p<0.001). Table 2 presents the perioperative, postoperative, and follow-up characteristics of the patients in the two groups. The average tumor sizes of the patients during surgery in the NAC/IDS and PDS arms were 5.5±3.6 and 9.4±4.8 cm, respectively (p<0.001). We investigated the presence of omental cake in both groups. Omental caking was reported in 68 patients (81%) in the NAC/IDS group and in 160 patients (76.9%) in the PDS group (p=0.53).

A total of 42 (50%) patients in the NAC/IDS group and 79 (28%) in the PDS group received blood transfusions. There was no statistically significant difference in the need for perioperative transfusions between the two groups (p=0.061). The average duration of surgery for all cases was 164.5±61.7 min in the NAC/IDS group and 172.8±55.9 min in the PDS group (p=0.058). Optimal cytoreduction was achieved in 34.5% of patients (N=29) in the NAC/IDS group and in 32.2% of patients (N=69) in the PDS group (p=0.825). Of the 208 patients in the PDS group, 26 (12.5%) underwent the following extensive and/or additional surgical procedures: 4 (1.9%) hepatic metastasectomies, 13 (6.2%) bowel resections, 9 (4.3%) splenectomies, 2 (0.9%) distal pancreatectomies, and 3 (1.4%) peritonectomies combined with HIPEC. In contrast, only 5 of 84 patients (5.9%) in the NAC/IDS group underwent extensive and/or additional surgical procedures (1 hepatic metastasectomy, 1 splenectomy, 1 bowel resection, and 3 peritonectomies combined with HIPEC).

The rate of patients requiring postoperative intensive care was 39.3% inthe NAC/IDS group and 40.1% in the PDS group (p=0.898). The average duration of hospital stay among the patients was 10.9±5.1 days in the NAC/IDS group and 9.81±4.7 days in the PDS group, which was a statistically significant difference (p=0.011).

The mean PFS was 40.2±7.6 months (range 1-128) in the NAC/IDS group and 40.4±5.0 months (range 1-160) in the PDS group. No statistically significant difference was found in PFS between

Table 2. Perioperative, postoperative, and follow-up characteristics of the patients in the two groups

Characteristics	*NAC/IDS group (N=84) N (%)*	*PDS group (N=208) N (%)*	*p value*
Omental cake	68 (81.0)	160 (76.9)	0.53
Cytoreduction			0.89
Suboptimal	55 (65.5)	139 (66.8)	
Optimal	29 (34.5)	69 (33.2)	
Tumor size (cm)	5.5 ± 3.6	9.4 ± 4.8	<0.001
Amount of ascitic fluid (mL)			0.25
≤500	15 (19.9)	55 (26.4)	
>500	69 (82.1)	153 (73.6)	
Duration of surgery (min)	164.5 ± 61.7	172.8±55.9	0.35
Blood transfusion requirements	42 (50)	79 (28)	0.06
Postoperative intensive care unit need	33 (39.3)	83 (40.1)	0.89
Duration of hospital stay (days)	10.9 ± 5.1	9.8 ± 4.7	0.01
Postoperative complications			0.786
Grade 3	2 (2.3)	7 (3.3)	
Grade 4	-	1 (0.5)	
Grade 5	2 (2.3)	5 (2.4)	
Total grade 3-5	4 (4.6)	13 (6.2)	
Progression-free survival (months)(range)	40.2 (1-128)	40.4 (1-160)	0.96
Overall survival (months)(range)	48.2 (1-128)	57.7 (1-160)	0.14
5-year expected PFS probability (%)	25.20	25.04	0.82
5-year expected OS probability (%)	23.73	36.22	0.02

Values for continuous variables are means ± SD or medians [minimum-maximum]. Values for categorical variables are the number/total number of cases (%). A p value <0.05 was considered to be statistically significant.NAC/IDS : Interval debulking surgery after neoadjuvant chemotherapy, PDS: Primary debulking surgery, PFS: progression-free survival, OS: overall survival

the NAC/IDS and PDS groups (p=0.961) (Figure 1). The mean OS was 48.2±5.8 months (range 1-128) in the NAC/IDS group and 57.7±3.7 months (range 1-160) in the PDS group, which was not a significant difference (p=0.142) (Figure 2). The 5-year expected PFS probability was 25.20% in the NAC/IDS group and 25.04% in the PDS group (p=0.82). The 5-year expected OS probability was 23.73% in the NAC/IDS group and 36.22% in the PDS group (p=0.027) (Table 2, Figures 1 and 2).

Multivariate analysis confirmed that treatment method, amount of ascitic fluid, and optimal cytoreduction rates were the independent risk factors that affected PFS and OS. The patients in the study were divided into two subgroups: 70 patients had an ascites volume of ≤ 500 mL, and 222 a volume of >500 mL. The PFS was 61.1±10.8 and 33.4±3.8 months in the groups with ascites volumes of ≤ 500 and >500 mL, respectively (p=0.01), while the OS was 71.1±8.2 and 51.3±3.3 months in the two groups, respectively (p=0.02). We found that the most significant predictive factor for PFS and OS was optimal cytoreduction (p<0.001 and p<0.001, respectively) (Table 3).

Discussion

EOC remains the leading cause of death among women who develop cancers of gynecologic origin [1]. In 75% of the cases, the patients have advanced-stage disease and distant metastases at the time of diagnosis due to the late and insidious onset of symptoms [12]. Therefore, it is important to determine the most appropriate treatment strategies for patients with advanced-stage ovarian cancer.

The use of neoadjuvant chemotherapy in the treatment of advanced EOC is still controversial. While primary cytoreductive surgery is the standard approach for the initial treatment of early-stage disease, the choice between primary surgery and neoadjuvant chemotherapy for the treatment of patients with advanced-stage (stages IIIC and IV) disease is not clear [13]. Vergote and colleagues

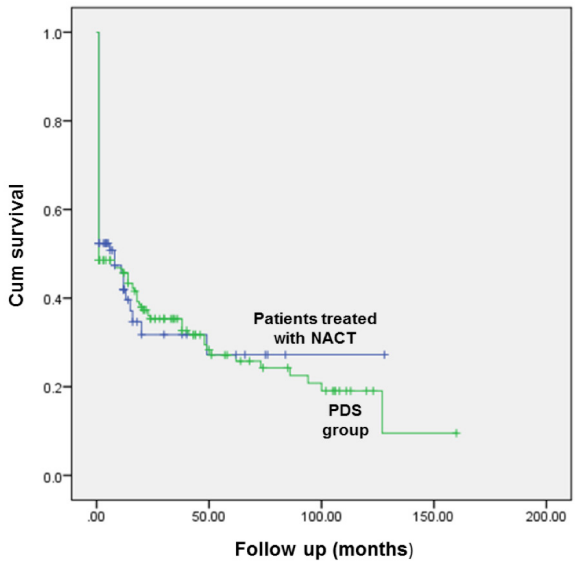

Figure 1. Kaplan-Meier survival curve showing the progression-free survival rates of patients in the NAC/IDS and PDS groups (p=0.961).

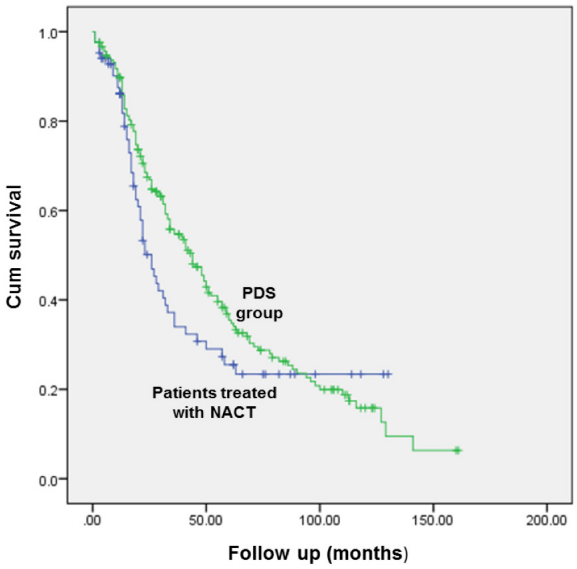

Figure 2. Kaplan-Meier survival curve showing the overall survival rates of patients in the NAC/IDS and PDS groups (p=0.142).

Table 3. Multivariate analysis of factors that affect the progression-free survival and overall survival using logistic regression models

Factors	*Estimated relative risk*		*95% Confidence interval*		*p value*	
	PFS	*OS*	*PFS*	*OS*	*PFS*	*OS*
Treatment modality (PDS vs NAC/IDS)	1.00	1.44	0.72 - 1.39	1.04 - 2.01	0.97	0.02
Ascites volume (≤500 vs >500 mL)	1.49	1.58	1.03 - 2.16	1.09 - 2.27	0.03	0.01
Surgical optimality (suboptimal vs optimal)	4.28	4.21	2.72 - 6.74	2.72 - 6.53	<0.001	<0.001

A p value <0.05 was considered to be statistically significant.NAC/IDS: Interval debulking surgery after neoadjuvant chemotherapy. PDS:primary debulking surgery. PFS: progression free survival, OS: overall survival

compared the survival rates of patients who were treated before and patients who were treated after the introduction of neoadjuvant chemotherapy in 1989. It was concluded that the treatment of a specific subgroup of patients with neoadjuvant chemotherapy was superior to the treatment of all patients with primary surgery [14]. A meta-analysis by Bristow and Chi in 2006 revealed that NAC, rather than primary surgical cytoreduction, was associated with a worse prognosis [6]. Another meta-analysis by Tangjitgamol et al. in 2010 indicated that there was no conclusive evidence to determine whether NAC would improve or decrease survival rates among women with advanced ovarian cancer compared with primary surgery [15]. The reasons for the heterogeneity of the results in these studies may be the difference in the severity of disease of the patients and the qualifications of surgeons in different studies.

Many studies have demonstrated that NAC/IDS effectively increases the feasibility of optimal cytoreductive surgery in advanced EOC [3-5,16]. While optimal cytoreduction was defined as a residual tumor of <1.0 cm in diameter in some of these studies, it was defined as <2.0 cm in the rest of the studies.In our study, there was no statistically significant difference in the optimal cytoreduction rates between the NAC/IDS and PDS

groups. Our study demonstrated superior survival rates in the patients of both groups who underwent optimal cytoreductive surgery.

The most important question to be asked here is whether NAC/IDS is superior to PDS with respect to survival. In many studies, similar survival rates between these two treatment modalities were reported [3,5,17]. In contrast, in a recent study by Taskin et al. significantly better survival rates were reported in the PDS group [18]. In an exploratory analysis conducted by the European Organisation for Research and Treatment of Cancer (EORTC) 55971 randomized trial, it was reported that patients in the NAC/IDS group had a slightly higher survival rate than patients in the PDS group. However, the difference was not statistically significant. Although there was no significant difference in response to neoadjuvant chemotherapy vs primary surgery among patients with stage IIIC disease, among patients with stage IV disease, the NAC/IDS group had a significantly higher 5-year survival rate than the PDS group. As a result, the clinical stage before the initiation of treatment may be informative in the selection of patients for either PDS or NAC/IDS. In this study, the clinical stage was found to be significantly associated with the benefit from neoadjuvant chemotherapy [19]. The strikingly low PFS and OS in the PDS arm of the EORTC-NCIC trial served as the impetus for another study to be performed [20]. In that study, a similar population to that of the EORTC-NCIC trial was selected to compare survival outcomes using a generally more extensive surgical approach than PDS. The survival outcomes were substantially better than those in the PDS arm of the EORTC-NCIC trial. It was emphasized in that study that the improved survival was due to the higher rate of optimal cytoreduction (71 vs 42%). Our reported median PFS and OS rates among patients in both groups were in alignment with the values in the contemporary literature. In contrast, a study published in 2001 concluded that patients with stage IIIC disease and a large ascites volume (>500 mL) had a significantly longer median survival rate and a higher resection rate in the NAC/IDS groupthan those in the PDS group [4]. There are numerous possible factors and explanations for the various survival results found in the literature, including tumor extent, surgical expertise, and patient selection. While standard chemotherapy regimens are used most often, surgical expertise and outcomes can vary among different countries, institutions, and surgeons [21-24]. A large amount of research has been performed, and although no consensus has been reached regarding the optimal number of NAC courses, 3 cycles of administration have generally been found to be effective [25,26].

According to the literature, although no survival advantage is offered by NAC/IDS, this treatment method provides favorable perioperative morbidity. Some studies reported that patients who underwent NAC/IDS had a lower estimated blood loss and a shorter hospital stay [5,27,28]. Unlike these studies, we found that patients in the NAC/IDS group had a longer hospital stay. This result may be due to a significantly higher number of patients with comorbidities and advanced age in our NAC/IDS group. We also found no difference in perioperative morbidity and in the perioperative blood transfusion requirement rates between the groups.

Some studies found that omental involvement with upper abdominal disease based on the preoperative CT (computerized tomography) scan is a predictor of suboptimal surgery [29,30] and is also an independent negative prognostic predictor of primary chemotherapy resistance and survival [31]. This finding may indirectly reflect an aggressive tumor biology and/or poor chemotherapy penetration in patients with large metastatic lesions. In one study, it was demonstrated that patients with extensive omental metastases were less likely to demonstrate adequate response to NAC. A large metastatic tumor in the upper abdomen may cause high proximal small bowel obstructions, which may lead to serious problems that can be difficult to control and palliate. Therefore, it is suggested that patients with extensive omental involvement should be treated with primary cytoreductive surgery instead of NAC/IDS [32]. We did not observe a significant difference in the number of patients who had omental cake between the two groups. However, we observed a significant difference when we divided all the patients into two separate groups, regardless of which treatment they received, namely, patients with ascitic fluid volume ≤ 500 mL and patients with ascitic fluid volume >500 mL. The patients with ascitic fluid volume ≤ 500 mL had a significantly longer median PFS and OS.

The selection of patients who are ideal candidates for NAC is very important. If optimal cytoreduction is not feasible with PDS, NAC/IDS may be another treatment option. One question remaining is whether we can predict a positive response to NAC. The exact answer to this question is not known because there are still controversies and

dilemmas pertaining to this issue [32]. Response to NAC can be evaluated by serum CA 125 levels. CA 125 is a good surrogate marker for tumor response, and patients with normalized CA 125 after NAC had bettersurvival rates [33]. In our study, the median serum CA 125 level was significantly higher in patients in the NAC/IDS group. In addition, the decrease in the median CA 125 level after chemotherapy was significant in patients in the NAC/IDS group.

The limitations of this study are as follows: its retrospective nature, the fact that some of the patients were treated by non-gynecological oncologic surgeons, and the 18-year time span. Retrospective cohort studies are subjected to selection bias, recall bias, and unknown confounding variables that may have a negative impact on the accuracy of the results. Besides, in patients with advanced age comorbidities are more prevalent in the NAC/IDC group leading thus to another bias. Moreover, during the 18-year period over which our study took place, significant improvement in surgical techniques, patient care, and adjuvant therapy, such as chemotherapy regimens, may also have affected the results.

In conclusion, PDS followed by chemotherapy remains the standard of care for women with stage IIIA and IIIB ovarian cancer. However, the choice between PDS and NAC/IDS is not clear for patients with stage IIIC and IV disease. In our study, there was no definitive evidence regarding whether neoadjuvant chemotherapy increases or decreases survival rates compared with primary surgery. Until new studies demonstrate the superiority, or at least the lack of inferiority, of the NAC approach, NAC should be reserved for patients who are deemed unsuitable for cytoreductive surgery as an initial treatment and who do not have access to a qualified gynecological oncologist.

Acknowledgements

The authors would like to thank Muzaffer Bilgin from the Department of Biostatistics of the Eskisehir Osmangazi University Faculty of Medicine for his assistance with statistical analysis.

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