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ORIGINAL REPORT

Phase III Trial of Doxorubicin With or Without Cisplatin in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study

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ABSTRACT

Purpose
Doxorubicin and cisplatin have activity in endometrial carcinoma and at initiation of this study ranked as the most active agents. This trial of stage III, IV, or recurrent disease evaluated whether combining these agents increases response rate (RR) and prolongs progression-free survival (PFS) and overall survival (OS) over doxorubicin alone.

Patients and Methods
Of 299 patients registered, 281 (94%) were eligible. Regimens were doxorubicin 60 mg/m^2 intravenously or doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks until disease progression, unacceptable toxicity, or a total of 500 mg/m^2 doxorubicin.

Results
There were 12 (8%) complete (CR) and 26 (17%) partial responses (PR) among 150 patients receiving doxorubicin versus 25 (19%) CRs and 30 (23%) PRs among patients receiving the combination. The overall response rate was higher among patients receiving the combination (42%) compared with patients receiving doxorubicin (25%; $P = .004$). Median PFS was 5.7 and 3.8 months, respectively, for the combination and single agent. The PFS hazard ratio was 0.736 (95% CI, 0.577 to 0.939; $P = .014$). Median OS was 9.0 and 9.2 months, respectively, for the combination and single agent. Overall death rates were similar in the two groups (hazard ratio, 0.928; 95% CI, 0.727 to 1.185). Nausea, vomiting, and hematologic toxicities were common. The combination produced more grade 3 to 4 leukopenia (62% *v* 40%), thrombocytopenia (14% *v* 2%), anemia (22% *v* 4%), and nausea/vomiting (13% *v* 3%).

Conclusion
Adding cisplatin to doxorubicin in advanced endometrial carcinoma improves RR and PFS with a negligible impact on OS and produces increased toxicity. These results have served as a building block for subsequent phase III trials in patients with disseminated and high-risk limited endometrial carcinoma.

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INTRODUCTION

In the United States, endometrial carcinoma is the most common invasive malignancy of the female genital tract.[1] It has a well-earned reputation for a very favorable prognosis resulting from the fact that, at presentation, 75% of cases are stage I and an additional 13% are stage II. Most patients with stage I or II disease achieve cure with surgical resection. Although there may have been a recent shift away from this treatment approach, historically (even for those patients with more advanced or recurrent disease) progestins were routinely used as systemic therapy because endometrial carcinoma was regarded as a hormonally responsive disease. These facts slowed the development of effective cytotoxic chemotherapy for the disease. Despite this, by the early 1990s, the

Gynecologic Oncology Group (GOG) had identified at least two active agents, doxorubicin and cisplatin, resulting from a series of concerted phase II trials initiated in 1976 (the activity of taxanes was not identified until later). In the absence of any evidence to support the routine use of combination chemotherapy in endometrial carcinoma, the GOG initiated a phase III randomized trial comparing doxorubicin, the single agent with the highest reported response rate,[2] with a combination of that agent plus cisplatin, another active agent.[3] The results of this trial led to a series of studies in both disseminated and limited high-risk endometrial carcinoma to establish a firm role for chemotherapy in both settings. Further, it formed the basis for the regimen currently used as the chemotherapy arm in studies of the treatment of optimally debulked stage III and IV disease.[4,5] The following report presents the detailed final results of this critical trial, GOG Protocol 107, for the first time.

PATIENTS AND METHODS

Eligibility Criteria

Patients were to have histologically documented stage III, IV, or recurrent endometrial carcinoma after prior surgery and/or radiotherapy. Disease was to be measurable and patients were to have had no prior cytotoxic chemotherapy (although they may have been treated with hormonal or one prior biologic therapy). Pretreatment laboratory assessment included a leukocyte count greater than 3000/μL, a platelet count greater than 100,000/μL, creatinine less than 2.0 mg/dL, and AST, alkaline phosphatase, and bilirubin less than twice normal. In addition, patients must have exhibited a GOG performance status of 0 to 2 (equivalent to a Karnofsky score of 50% or better), with no contraindication to the use of cisplatin, no history of congestive heart failure or abnormal cardiac compensation, and no history of a previous invasive malignancy other than skin cancer (excluding melanoma). Multiple-gated acquisition scans were required to document a normal ejection fraction before study entry. All patients provided signed informed consents consistent with Federal, State, and local regulations before entering the study. From each patient, hematoxylin and eosin stained slides representative of the primary tumor and metastatic tumor were to be submitted and reviewed centrally by two members of the GOG Pathology Committee. Disagreements regarding eligibility were arbitrated by a third pathologist if necessary. These reviews were blinded to the treatment outcomes.

Treatment

Patients were randomly assigned to receive either doxorubicin 60 mg/m^2 intravenously every 3 weeks or doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2, both intravenously, every 3 weeks with appropriate hydration. Patients older than 65 years and/or those completing external radiation therapy before entering the study initiated doxorubicin at 45 mg/m^2 and were to be escalated to 60 mg/m^2 on the second cycle, provided they experienced no toxicity worse than grade 1. Also, those individuals who entered the study with hepatic dysfunction manifested as bilirubin between 1.1 and 3.0 mg/100 mL started doxorubicin at 30 mg/m^2 and escalated to 45 mg/m^2 and 60 mg/m^2, provided they experienced no toxicity greater than grade 1. Reassessment was performed at the time of each treatment and therapy was to be continued until unacceptable toxicity intervened, progression of disease occurred, the patient died or was lost to follow-up, or a cumulative dose of 500 mg/m^2 doxorubicin was administered.

End Points

The analysis of this trial included examination of several aspects: pretreatment characteristics of the patients, assessment of objective response as well as progression-free survival (PFS) and overall survival, and evaluation of toxicity on each of the two regimens. Response was defined according to standard GOG criteria as follows: complete response (CR) required disappearance of all evidence of disease for at least 1 month. Partial response (PR) necessitated a reduction of at least 50% in the product of perpendicular diameters of each and every measurable lesion, with no appearance of a new lesion, for at least 1 month. Stable disease was defined as less than a 50% change in the product of perpendicular diameters of each and every measurable lesion and no appearance of a new lesion for at least 1 month. Increasing disease indicated that one or more lesions had demonstrated at least a 50% increase in the product of perpendicular diameters or that one or more new lesions had appeared within 1 month of initiating therapy.

PFS was defined as the time from entry onto study to evidence of first disease progression, death, or date of last contact, if the patient was alive and progression-free. Overall survival was assessed as the date the patient was registered onto the study to the date of death, regardless of cause, or the date of last contact, if the patient was alive.

Toxicity was graded according to the GOG Common Toxicity Criteria.[6]

Statistical Considerations

All patients enrolled onto this study were registered centrally in the GOG Statistical and Data Center before initiating study treatment. The randomized study treatment was not revealed until registration was complete, and this report provides an accounting of all patients registered onto the study. The study regimens were sequentially drawn from preallocated lists of treatments randomly permuted and balanced within blocks. Separate treatment allocation lists were maintained for each GOG member institution.

On the basis of an expected response rate to doxorubicin of 22% (that was seen in GOG Protocol 48), the study sought to identify an increase of 15% in response rate to 37%. The planned sample size of 140 eligible patients enrolled onto each treatment group permits an 84% chance of detecting this size treatment effect with a one-sided test of significance at the .05 level. Provided that at least 75% of the patients experienced progression or death, this sample size also permits a 90% chance of detecting a treatment that effectively increases median duration of PFS or overall survival by 50% when the type I error is set to .05 for a one-tail test. The statistical test of independence between randomly assigned treatment and time-to-event outcomes was assessed with a Cox's proportional hazards model adjusted for initial performance status.[7] In this report, all significance tests are two-tailed. The primary treatment comparisons of benefit include all eligible patients, regardless of the amount of study treatment received. Both eligible and ineligible patients are included in the analyses and compared by treatment assignment when an intent-to-treat analysis is specifically indicated in this article. The summaries of toxicity include all patients who received any study treatment;

those who did not receive study treatment are not included in these summaries.

RESULTS

Patient Characteristics

GOG member institutions entered 299 patients with advanced or recurrent endometrial carcinoma onto this study. Of these, 18 were ineligible on detailed quality control review because of the following: synchronous ovarian primary tumor (three patients), primary other than endometrial carcinoma (nine patients), uncertain origin of primary tumor (three patients), ineligible cell type (two patients), and inadequate pathology materials for review (one patient). Of the 281 eligible patients, 278 received the designated study agent(s) and were evaluated for toxicity. Patient characteristics of the 281 eligible patients are listed in Table 1. The median age is 66.9 years and 64.4 years for patients on the single-agent and combination regimens, respectively. Most patients (65%) had prior radiotherapy and 32% had prior hormonal therapy.

The median and interquartile range of the doxorubicin dose delivered during the first course of treatment was 45 mg/m^2 (range, 44.7 to 55.3 mg/m^2) and 45 mg/m^2 (range, 44.7 to 59.2 mg/m^2) for patients randomly assigned to the single-agent and combination regimen, respectively. These doses reflect the fact that most patients were started at the lower doxorubicin dose per protocol because of age older than 65 years or having had prior radiation therapy. There were three eligible patients who did not receive any of their assigned study treatment. The number of courses of study treatment delivered is summarized in Table 2 by randomly assigned treatment group.

Table 1. Patient Characteristics (N = 281)

Characteristic	Doxorubicin (n = 150) No. of Patients	%	Doxorubicin + Cisplatin (n = 131) No. of Patients	%
Age, years				
< 50	7	5	10	8
50-59	33	22	29	22
60-69	58	38	49	37
70-79	48	32	38	29
≥ 80	4	3	5	4
Race				
Black	17	11	17	13
Hispanic	1	1	2	2
Asian	1	1	1	1
White	127	85	108	82
Other	4	3	3	2
Performance status				
0	53	35	50	38
1	72	48	52	40
2	25	17	29	22
Histologic grade				
1	27	18	29	22
2	51	34	35	27
3	72	47	67	51
Cell type				
Endometrioid	74	49	61	47
Serous	23	15	22	17
Adenosquamous	24	16	17	13
Adenoca, not specified	14	9	17	13
Clear cell	9	6	6	5
Other	6	4	8	6
Prior radiotherapy	93	62	89	68
Prior hormonal therapy	44	29	46	35

Response

Clinical response is summarized in Table 3 for 281 eligible patients. Twenty patients did not have repeat tumor measurements for response assessment. In four patients receiving doxorubicin and in six patients receiving doxorubicin plus cisplatin, death or significant physical deterioration precluded disease reassessment. In the remaining 10 patients (five in each regimen), excessive toxicity or patient refusal precluded disease reassessment. All of these cases are included in Table 3 as having no clinical response. There were 37 CRs and 56 PRs, for an overall response rate of 33%. Among those patients who were randomly assigned to doxorubicin plus cisplatin, there were 25 CRs (19%) and 30 PRs (23%), whereas among those randomly assigned to single-agent doxorubicin, there were 12 CRs (8%) and 26 PRs (17%). The superior response rate (CR plus PR) observed in the combination regimen was statistically significant ($P = .004$). The percentage of CRs was also higher for the combination regimen ($P = .008$).

PFS and Overall Survival

PFS is depicted graphically in Figure 1. Patients who received the combination regimen demonstrated longer PFS on average when compared with those who received single-agent doxorubicin, with a median of 5.7 versus 3.8 months. After adjusting for the initial performance status, the estimated hazard rate of first progression or death on the

Table 2. Courses of Study Therapy

No. of Courses	Doxorubicin (n = 150) No. of Patients	%	Doxorubicin + Cisplatin (n = 131) No. of Patients	%
0	1	1	2	2
1-2	43	29	28	21
3-5	51	34	37	28
6-10	50	33	59	45
≥ 10	5	3	5	4

Table 3. Response (N = 281)

Response	Doxorubicin (n = 150) No. of Patients	%	Doxorubicin + Cisplatin (n = 131) No. of Patients	%
Complete response	12	8	25	19
Partial response	26	17	30	23
No response	112	75	76	58

combination regimen is 0.736 (95% CI, 0.577 to 0.939; $P = .014$) times the rate on the single-agent regimen. The estimated hazard ratio is 0.748 when all eligible and ineligible (n = 299) patients are included for an intent-to-treat analysis.

Overall survival is shown in Fig 2. Overall survival for each regimen was similar, with a median of 9.0 months for the combination arm versus 9.2 months for the single-agent arm. After adjusting for the initial performance status, the death rate on the combination regimen was 0.928 times (95% CI, 0.727 to 1.185) the death rate observed on the single-agent regimen. The estimated hazard ratio for the intent-to-treat analysis is 0.953. Neither of these analyses indicates a significant difference between treatment groups in overall survival.

Adverse Effects

As shown in Table 4, hematologic adverse effects manifesting as leukopenia, thrombocytopenia, and anemia were common. Leukopenia was more common in the combination therapy, with 84% versus 72% (all grades) and 62% versus 40% (grade 3 to 4). Although less problematic than leukopenia, thrombocytopenia was also observed with more frequency and severity in the combination arm: 50% versus 17% (all grades) and 14% versus 2% (grade 3 to 4). A similar effect was seen with anemia: 69% versus 42% (all grades) and 22% versus 4% (grade 3 to 4). Nausea and vomiting were also often reported, with greater frequency and severity in the combination arm: 50% versus 30% (all grades) and 13% versus 3% (grade 3 to 4). Renal toxicity was reported more frequently among those on the combination arm: 10% versus 0% (all grades).

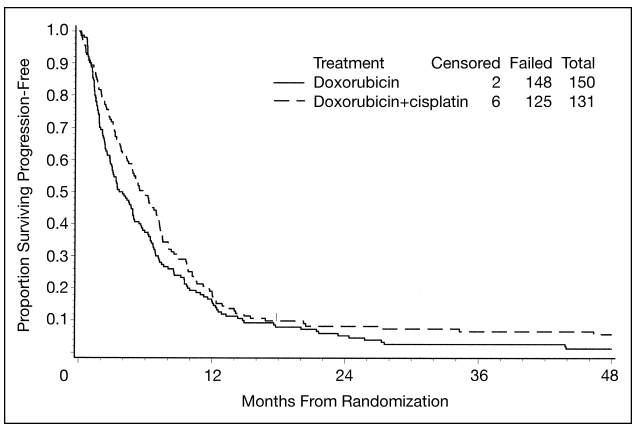

Fig 1. Progression-free survival by treatment group.

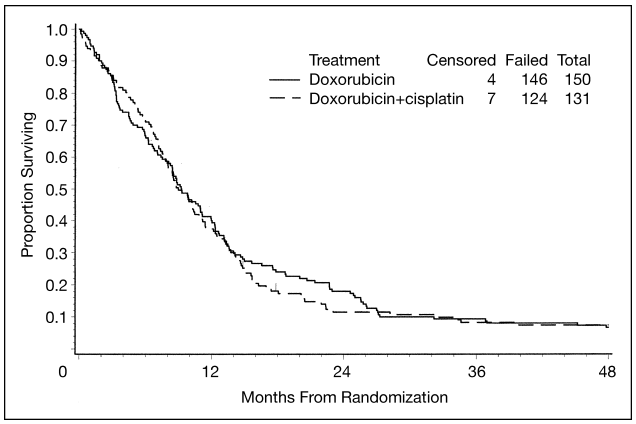

Fig 2. Overall survival by treatment group.

DISCUSSION

In 1976, only three cytotoxic agents had exhibited potential activity in endometrial carcinoma on the basis of data collected from broad phase II trials: fluorouracil, cyclophosphamide, and doxorubicin.[1] At that time, the GOG and others initiated efforts to evaluate single agents in phase II trials, eventually completing studies of 29 drugs over the ensuing 25 years.[2,3,8-23] Among them, the anthracyclines doxorubicin and epirubicin, the platinum analogs cisplatin and carboplatin, and paclitaxel, vincristine, and fluorouracil, have shown phase II evidence of significant activity, with response rates ≥ 15%. The agents with the highest response rates include the anthracyclines, the platinum compounds, and paclitaxel, as illustrated in Table 5.[2,3,8-23] By 1988, only doxorubicin and the platinum compounds had shown evidence of significant activity, and most efforts to evaluate combination regimens in the treatment of endometrial carcinoma consisted of small, uncontrolled series without opportunity to assess the relative merits of combination and single-agent therapy.[24]

During that 25-year period, the GOG also conducted six randomized trials (five in addition to the current report) seeking to identify effective combinations of chemotherapy for the treatment of this disease (Table 6).[25-29] The first, based on two promising pilot studies, randomly assigned patients to megestrol acetate plus either cyclophosphamide, doxorubicin, and fluorouracil or melphalan plus fluorouracil.[25] Although the pilot results were encouraging, the phase III comparison (Table 6) revealed insignificant differences in response rates, PFS, and overall survival, and

Table 4. Adverse Effects by Treatment Arm (n = 278)

		Grade							
		1		2		3		4	
Adverse Effect	Regimen	No.	%	No.	%	No.	%	No.	%
Leukopenia	Dox	19	12.8	28	18.8	49	32.9	11	7.4
	Dox + Cis	7	5.4	21	16.3	44	34.1	36	27.9
Thrombocytopenia	Dox	21	14.1	1	0.7	2	1.3	1	0.7
	Dox + Cis	36	27.9	11	8.5	11	8.5	7	5.4
Anemia	Dox	29	19.5	28	18.8	6	4.0	0	0.0
	Dox + Cis	15	11.6	45	34.9	25	19.4	4	3.1
Nausea/vomiting	Dox	21	14.1	20	13.4	4	2.7	0	0.0
	Dox + Cis	14	10.9	35	27.1	13	10.1	4	3.1
Other gastrointestinal	Dox	8	5.4	13	8.7	4	2.7	1	0.7
	Dox + Cis	11	8.5	12	9.3	8	6.2	2	1.6
Renal	Dox	0	0.0	0	0.0	0	0.0	0	0.0
	Dox + Cis	7	5.4	3	2.3	1	0.8	2	1.6
Cardiac	Dox	7	4.7	15	10.1	4	2.7	2	1.3
	Dox + Cis	2	1.6	14	10.9	5	3.9	2	1.6
Neurologic	Dox	7	4.7	1	0.7	1	0.7	0	0.0
	Dox + Cis	7	5.4	6	4.7	0	0.0	0	0.0
Infection/fever	Dox	2	1.3	13	8.7	0	0.0	0	0.0
	Dox + Cis	1	0.7	8	6.2	7	5.4	1	0.7

Abbreviations: Dox, doxorubicin (n = 149); Dox + Cis, doxorubicin + cisplatin (n = 129).

results were similar to those reported with single agents.[25] The second GOG phase III trial randomly assigned patients to doxorubicin with or without cyclophosphamide (Table 6).[26] Among 202 patients with measurable disease, doxorubicin yielded a response rate of 22% and a median survival of 6.8 months versus 32% and 7.6 months, respectively, for the combination; thus the combination offered no advantage over single-agent therapy.[26]

The subject of the current report was the third among the six GOG randomized trials and the first to demonstrate some advantage to combination chemotherapy. As presented in Results, doxorubicin plus cisplatin increases the proportion of responding patients and prolongs PFS (Table 3, Figs 1 and 2), although these improvements exact more toxicity in the form of myelosuppression and gastrointestinal effects (Table 4).

Table 5. Single Agents Active Against Endometrial Carcinoma[21,23] (response rate ≥15%)

Agent	No. of Responses	No. of Patients	%
Doxorubicin	20	64	31
Epirubicin	7	27	26
Cisplatin	25	86	29
Carboplatin	16	52	31
Paclitaxel	22	72	31
Vincristine	6	38	16
Fluorouracil	7	34	21

Since completing this study, the GOG has conducted three additional phase III randomized trials. The first compared standard-timed doxorubicin plus cisplatin as reported herein to a circadian-timed regimen of the same two drugs, administering doxorubicin at 6 AM and cisplatin at 6 PM on day 1 of each 3 weeks (Table 6).[27] The second compared doxorubicin plus cisplatin as reported in this article with doxorubicin 50 mg/m^2 plus paclitaxel 150 mg/m^2/24 hours plus granulocyte colony-stimulating factor, finding no significant differences in response rates, PFS, or overall survival (Table 6). Toxicity favored the doxorubicin plus cisplatin combination.[28] In the third trial, patients were randomly assigned to either doxorubicin plus cisplatin or an aggressive combination of doxorubicin plus cisplatin plus paclitaxel (Table 6).[29] It is important to note that the subject of this report, doxorubicin plus cisplatin as defined by GOG Protocol 107, was selected as the control arm in the three most recent GOG randomized trials.

Several additional points are noteworthy. First, some contend that carboplatin should be substituted for cisplatin, because carboplatin seems to have similar activity as a single agent. This is not unreasonable. However, given that the three-drug combination in the most recently completed GOG study (Protocol 177) demonstrated improvement in response and survival compared with the doublet,[4] the substitution of carboplatin might create problems related to excessive myelosuppression. Such a three-drug combination should be piloted first. In

Table 6. Summary of Response and Survival in Five GOG Randomized Trials

GOG Study/Regimen	Response (CR + PR) No.	Response (CR + PR) %	Median Survival (months)	Reference
Protocol 28				25
Melphalan + FU + megace	29/77	38	10.6	
Doxorubicin + FU + cyclophosphamide + megace	28/78	36	10.1	
Protocol 48				26
Doxorubicin	22/97	22	6.8	
Doxorubicin + cyclophosphamide	34/105	32	7.6	
Protocol 139				27
Doxorubicin + cisplatin (standard timed)	77/169	45	11.2	
Doxorubicin + cisplatin (circadian timed)	85/173	49	13.2	
Protocol 163				28
Doxorubicin + cisplatin + G-CSF	63/157	40	12.5	
Doxorubicin + paclitaxel + G-CSF	69/160	43	13.6	
Protocol 177				29
Doxorubicin + cisplatin	44/129	34	12.3	
Doxorubicin + cisplatin + paclitaxel + G-CSF	77/134	57	15.3	

Abbreviations: GOG, Gynecologic Oncology Group; CR, complete response; PR, partial response; FU, fluorouracil; G-CSF, granuloctye colony-stimulating factor.

lieu of studying what might be a very toxic three-drug carboplatin-based regimen, the GOG is currently randomly assigning patients with advanced (stage IVB) or recurrent disease to either the three-drug cisplatin-based regimen from Protocol 177 or to paclitaxel plus carboplatin to determine whether it is possible to drop doxorubicin from the regimen and substitute carboplatin for cisplatin without loss of efficacy and with a marked improvement in the toxicity profile (GOG Protocol 209). Second, improvements in response reported to date are not large, whereas there is notable increase in the observed toxicity. Some have argued that the trade-off between improved efficacy and increased toxicity is insufficient to justify the use of the more toxic combination. This is obviously an issue to be discussed with patients before the initiation of therapy.

In conclusion, this study demonstrates significant improvement in response rate and PFS when cisplatin is added to doxorubicin in the treatment of patients with advanced or recurrent endometrial carcinoma. An improvement in overall survival does not accompany the improvements in PFS and response rate, and the combination regimen does produce increased toxicity. The judgment of the investigators is that the magnitude of the increase in both the overall and complete response rates, as well as in PFS, is sufficient justification for the use of the combination. The importance of these observations is striking when viewed in terms of subsequent phase III studies of combination chemotherapy (as well as a phase III trial in patients with high-risk limited stage III to IVA disease) that used this doublet regimen as a building block. An even more recent example of its continuing relevance was reported at the Plenary Session of the 2003 Annual Meeting of the American Society of Clinical Oncology, which provided evidence from GOG Protocol 122 that this doublet administered after surgical bulk reduction in stage III to IVA disease produces superior PFS and overall survival when compared with surgery followed by abdominopelvic radiation.[5] This lends further support to the current article, in which the basis for establishing a firm role for combination chemotherapy in the management of endometrial carcinoma is first presented.

Appendix

The appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: J. Tate Thigpen, Bristol-Myers Squibb Co. Received more than $2,000 per year from a company for either of the last 2 years: J. Tate Thigpen, Bristol-Myers Squibb Co.

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