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Nationwide randomized comparative study of daunorubicin and aclarubicin in combination with behenoyl cytosine arabinoside, 6-mercaptopurine, and prednisolone for previously untreated acute myeloid leukemia

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Abstract. Aclarubicin was evaluated in combination chemotherapy for adult acute myeloid leukemia in a randomized trial involving 58 institutions throughout Japan. Behenoyl cytosine arabinoside (BH-AC)•daunorubicin, 6-mercaptopurine, and prednisolone (DMP) was compared with BH-AC•aclarubicin, 6-mercaptopurine, and prednisolone (AMP). In the 360 evaluable cases among the 433 cases enrolled, complete remission (CR) rates were 63.7% (116/182) for BH-AC•DMP and 53.9% (96/178) for BH-AC•AMP ($P = 0.0587$). Median survival periods and 7-year survival rates were 15.8 months and 19.3% for BH-AC•DMP and 9.5 months and 20.2% for BH-AC•AMP ($P = 0.0091$ according to the generalized Wilcoxon test [GW], $P = 0.196$ according the log-rank test [LR]). Median disease-free survival periods were 15.4 months for BH-AC•DMP and 14.1 months for BH-AC•AMP ($P = 0.851$ by GW, $P = 0.439$ by LR). Among the 346 cases of extramurally confirmed FAB subtypes, CR rates were 67.9% (19/28) with BH-AC•DMP and 31.8% (7/22) with BH-AC•AMP for subtype M3 ($P = 0.011$) and 63.3% (93/147) with BH-AC•DMP and 56.8% (84/148) with BH-AC•AMP ($P = 0.254$) for subtypes M1, M2, M4, and M5. Diarrhea, ileus, pneumonia, and renal failure were more frequent with BH-AC•AMP than with BH-AC•DMP. The results indicate, at least on the basis of the long-term outcome, that BH-AC•AMP has antileukemic effects on subtypes M1, M2, M4, and M5 that are comparable with those of BH-AC•DMP.

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Introduction

The present long-term study comparing two anthracyclines, daunorubicin (DNR) and aclarubicin (ACR), in multidrug therapy for adult acute myeloid leukemia (AML) patients who had not been previously treated was begun in 1983. Until that time, AML treatment, which principally involved combination regimens including DNR and cytosine arabinoside (ara-C), had led to complete remission (CR) rates as high as 60%–80%. However, most of the patients achieving a CR relapsed within 2–3 years and no more than 20%–30% survived for more than 5 years [4], suggesting that new antileukemia agents or new treatment strategies would be required for further improvement.

ACR was isolated from a culture of *Streptomyces galieaues* by Oki and colleagues in 1975 [21]. It was shown to have a stronger inhibitory effect on RNA synthesis than on DNA synthesis and to produce less cardiotoxicity than other anthracyclines [5, 26]. In its early clinical trials, it showed 18%–43% CR rates in AML patients when given as a single agent [3, 12, 14, 25, 22, 24, 27], indicating a reason

to evaluate it in combination therapy in comparison with other anthracyclines.

Behenoyl cytosine arabinoside (N^4-behenoyl-1-β-D-arabinofuranosylcytosine; BH-AC) is an ara-C analogue that is resistant to cytidine deaminase and exhibits strong, persistent cytotoxic activity against a wide variety of experimental tumors [1, 2]. In a phase II study, BH-AC produced a 36% CR rate in adult AML patients [11]. Combination therapy (BH-AC•DMP) consisting of BH-AC, DNR, 6-mercaptopurine (6MP), and prednisolone (PSL) was shown to produce an 82% CR rate in adult AML [20], and similar CR rates were reported for combination therapy (BH-AC•AMP) consisting of BH-AC, ACR, 6MP and PSL [7, 8].

The present randomized, prospective clinical study of BH-AC•DMP versus BH-AC•AMP for adult AML was therefore organized and begun in 1983. It was conducted by the nationwide Japanese Cooperative Study Group chaired by Dr. Kiyoji Kimura, formerly Director of Nagoya National Hospital. Preliminary reports of the study have been made elsewhere [17, 18]. We report herein the final results and conclusions.

Patients and methods

Patient population. Between April 1983 and March 1985, 433 patients with AML [French-American-British (FAB) classification: M1, M2, M3, M4, M5 and M6] were enrolled in this study at 58 institutions (see Appendix) located throughout Japan. Eligible patients were between 15 and 65 years old and had no prior treatment, no significant concomitant cardiac, renal, or hepatic disease, and no other malignancy. All enrollment was made with the informed consent of the patient and/or guardian.

Initial diagnosis of AML was made at each institution using hematological samples by Wright's or May-Grünwald-Giemsa staining and by special histochemical staining with agents such as peroxidase and/or Sudan black B. The hematological specimens of peripheral blood and bone marrow were also sent to an extramural FAB classification committee (chairman, Dr. Ichita Amaki, formerly Professor of the First Department of Internal Medicine, Nihon University School of Medicine) for confirmation of the FAB subtype diagnosis. Erythremia, refractory anemia with an excess of blasts (RAEB), and RAEB in transformation were excluded from this study. Patients were randomized at the Central Office of the Japanese Foundation for Multidisciplinary Treatment of Cancer.

Treatment protocol. The induction protocol for one course for M1, M2, M4, M5, and M6 patients consisted of a 10- to 14-day treatment of daily BH-AC (170 mg/m^2 daily, 2-h i.v.), daily 6MP (70 mg/m^2 daily p.o.), and daily PSL (20 mg/m^2 daily p.o.) for the patients of each arm, together with intermittent DNR (25 mg/m^2 daily bolus i.v., days 1 and 2; thereafter, as necessary to achieve the criteria described below) in the BH-AC•DMP arm (arm A) and daily ACR (14 mg/m^2 daily bolus i.v., 10–14 days) in the BH-AC•AMP arm (arm B). Hematological hypoplasia criteria for the termination of one course of the induction therapy were established, with the length of the course and the number of DNR administrations to be adjusted, depending on each patient's response to the therapy, so as to attain a peripheral white blood cell (WBC) count of 1,200/μl or lower and a nucleated cell count in bone marrow of 15,000/μl or lower, if possible within 10–14 days. As a general rule, two courses of the induction therapy were permitted to attain a CR. For acute promyelocytic leukemia (M3), the same doses of BH-AC, 6MP, and PSL shown above and higher doses of 40 mg/m^2 DNR (arm A) or 25 mg/m^2 ACR (arm B) were given daily, with 5–10 days comprising one course. Blood transfusions, antibiotics, and other intensive supportive-care measures were given vigorously.

The consolidation therapy for patients who had attained a CR consisted of two shortened courses of the same drug combination used in the induction regimen: BH-AC (170 mg/m^2 daily), 6MP (70 mg/m^2 daily), and PSL (20 mg/m^2 daily) for 7 days, together with DNR (25 mg/m^2 daily) on days 1 and 2 in arm A and ACR (14 mg/m^2 daily) for 7 days in arm B, and with intrathecal methotrexate (10 mg/m^2) being given twice between the two courses. Patients were discharged and followed as outpatients every 1–2 weeks, receiving maintenance therapy consisting of two regimens given alternately every 6 weeks for 2 years or until relapse. One of the two regimens was vincristine (1.4 mg/m^2 bolus i.v., 2 mg maximum, on days 1 and 8), cyclophosphamide (550 mg/m^2 drip infusion on days 1 and 8), 6MP (70 mg/m^2 p.o. for 2 weeks), and PSL (20 mg/m^2 p.o. for 2 weeks). The other regimen was 4–6 days of the same drug combination that was received in induction therapy.

Analytical method. Chemotherapeutic effects were evaluated by Kimura's criteria [10], with a CR being defined by normocellular bone marrow containing normal erythroid and granuloid series with $<5\%$ myeloblasts, accompanied by normal levels of peripheral WBC and platelet counts with no circulating blasts. A partial remission (PR) was defined by a myeloblast reduction in bone marrow to less than half the percentage observed at the initiation of therapy and by a reduction in the peripheral WBC to $<5\%$. A relapse was defined by the observation of blasts in bone marrow exceeding 5% or the histological detection of extramedullary leukemic invasion of the CNS or other organs. Disease-free survival (DFS) was defined as the time from the achievement of a CR to leukemic relapse or to death in CR, and the duration of survival was defined as the period from diagnosis to death. If the patient received bone marrow transplantation (BMT), DFS and survival time were censored at the time of BMT.

Statistical analysis. DFS and survival curves were calculated according to the Kaplan-Meier method. The chi-square test was applied to analyze patients' characteristics, remission rates, and toxicities. The generalized Wilcoxon test (GW) and the log-rank test (LR) were employed for the statistical analysis of DFS and survival periods. Statistical analyses were carried out at the Nagoya University Computation Center. The closing date for statistical evaluation was March 31, 1991.

Results

Evaluable patients

Of the 433 patients enrolled, 360 were evaluable. There was no statistically significant deviation in the dropout number or cause between the two arms. The FAB morphological diagnosis of 346 of the evaluable cases was confirmed by the extramural FAB classification committee, and statistical analysis concerning FAB subtypes was restricted to these 346 cases.

A profile of the patients at entry for all evaluable cases is given in Table 1. As shown, the median ages of patients in arm A and arm B were 42 and 45 years, respectively, and there was no significant difference between the two arms in age, sex, peripheral WBC count, FAB classification or in other characteristics such as red blood cell count, platelet count, findings of bone marrow analysis, or blood chemistry (data not shown).

For all confirmed M1, M2, M4, M5, and M6 subtypes, the median duration of BH-AC administration in the first course of induction therapy was 12 days (range, 3–29 days)

Table 1. Comparison of patients' characteristics

	BH-AC•DMP (arm A)	BH-AC•AMP (arm B)
Number of cases entered	217	216
Number of evaluable cases	182	178
Age (years):		
15–19	8	10
20–29	24	21
30–39	46	38
40–49	49	41
50–59	43	48
60–65	12	20
Median	42	45
M/F	95/87	88/90
WBC ($\times 10^4/\mu l$):		
0.99	79	81
1.0–2.99	38	37
3.0–4.99	21	20
≥5.0	44	40
FAB subtype[a]:		
M1	49	44
M2	69	72
M3	28	22
M4	19	24
M5	10	8
M6	0	1

[a] As confirmed by the extramural FAB classification committee

in arm A and 12 days (range, 3–21 days) in B. The median duration of 6MP administration in the first course was 12 days (range, 1–29 days) in arm A and 12 days (range, 3–20 days) in arm B. In both arms, PSL administration followed practically the same schedule used for BH-AC and 6MP. The DNR delivery numbers (number of administrations per patient and percentage of patients receiving that number) in the first course were 1 (0.6%), 2 (20.1%), 3 (8.4%), 4 (27.9%), 5 (22.7%), 6–7 (12.3%), and 8–13 (7.9%), and the DNR median total dose was 160 mg (range, 40–600 mg). The ACR delivery numbers were 3–7 (7.8%), 8–9 (13.0%), 10–12 (35.7%), 13–14 (25.3%), and 15–20 (18.2%), and the ACR median total dose was 240 mg (range, 60–525 mg). At the termination of the first course, 56.6% of the patients in arm A and 56.3% of those in arm B had attained a peripheral WBC count of 1,200/μl or lower, and 59.1% in arm A and 60.3% in arm B had attained a bone-marrow nucleated cell count of 15,000/μl or lower. The proportions of those attaining both criteria were 38.3% in arm A and 38.5% in arm B.

For the confirmed M3 subtype, the median durations of BH-AC and 6MP administration were 8 days (range, 5–15 days) in arm A and 9 days (range, 5–15 days) in arm B, respectively. The DNR delivery numbers were 5–7 (50.0%), 8–10 (28.6%), and 11–15 (21.4%), with a DNR median total dose of 355 mg (range, 80–630 mg). The ACR delivery numbers were 5–7 (36.4%), 8–10 (45.4%), and 11–15 (18.2%), with an ACR median total dose of 287 mg (range, 200–400 mg). Of all evaluable patients, 60.8% in arm A and 70.6% in arm B completed the induction therapy in one course. Three patients in each arm received a BMT.

Table 2. CR rates by FAB subtype

FAB subtype[a]	BH-AC•DMP (arm A)	BH-AC•AMP (arm B)
M1	26/49 = 53.1%	24/44 = 54.5%
M2	49/69 = 71.0%	43/72 = 59.7%
M3[b]	19/28 = 67.9%	7/22 = 31.8%
M4	13/19 = 68.4%	11/24 = 45.8%
M5	5/10 = 50.0%	6/ 8 = 75.0%
M6		1/ 1 = 100.0%

[a] As confirmed by the extramural FAB classification committee
[b] CR rate significantly higher for BH-AC•DMP than for BH-AC•AMP ($P < 0.011$)

Response and survival

A CR was attained by 116 (63.7%) of the 182 evaluable patients in arm A (BH-AC•DMP) and 96 (53.9%) of the 178 evaluable patients in arm B (BH-AC•AMP). The difference between these two CR rates was not statistically significant, although by a narrow margin ($P = 0.0587$).

The CR rates by confirmed FAB subtype are summarized in Table 2. No statistically significant difference in the CR rate was found between the two arms for M1, M2, M4, or M5 subtypes. For the M3 subtype, however, the CR rate was significantly higher in arm A than in arm B (19/28 = 67.9% vs 7/22 = 31.8%; $P = 0.011$). When the chemotherapeutic results for the confirmed M3 subtype are excluded from the CR rates for all confirmed subtypes, the CR rates in arm A and B amount of 63.3% (93/147) and 57.0% (85/149), respectively, with no statistically significant difference occurring between the two arms ($P = 0.275$).

The disease-free survival periods (DFS) of all patients who attained a CR in arms A and B are shown in Fig. 1. The median DFS values were 15.4 months in arm A and 14.1 months in arm B, and the 7-year DFS rates were 21.1% in arm A and 27.7% in arm B, with no statistically significant difference being observed between the two arms ($P = 0.851$ [GW], $P = 0.439$ [LR]). Within each subtype (M1, M2, M3, M4, M5), moreover, no statistically significant difference in DFS was found between the two arms (data not shown). Figure 2 shows the survival periods for all evaluable cases. The median value and 7-year rate were 15.8 months and 19.3% for arm A and 9.5 months and 20.2% for arm B. The difference between the survival curves was statistically significant as determined by GW ($P = 0.0091$) but not by LR ($P = 0.196$).

Adverse effects

During the induction therapy the frequencies of nausea or vomiting, abnormality of GPT, sepsis, gastrointestinal bleeding, elevation of bilirubin, diabetes mellitus, disseminated intravascular coagulopathy (DIC), ECG abnormality, and heart failure were much the same in both arms. However, higher frequencies of diarrhea (grades 3 and 4, 32% with BH-AC•AMP vs 9.2% with BH-

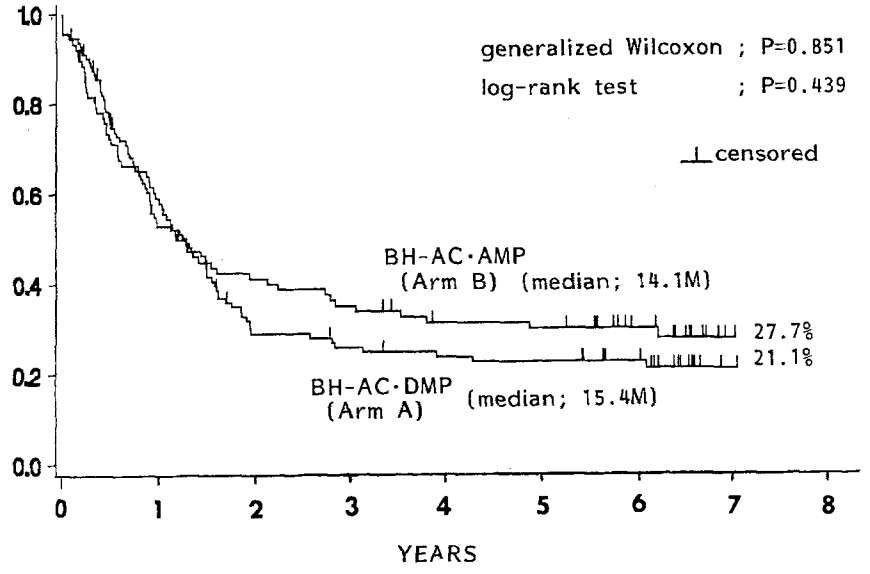

Fig. 1. Disease-free survival following the achievement of a CR

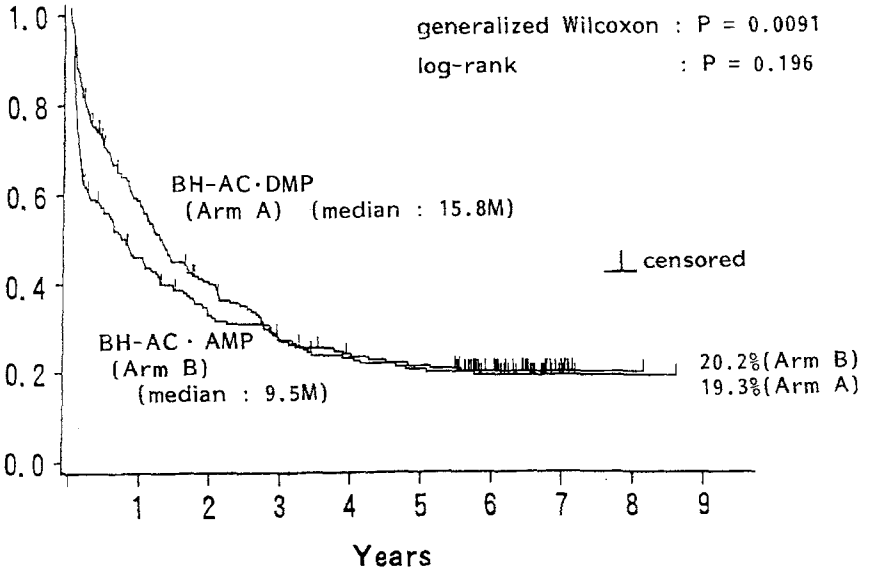

Fig. 2. Duration of survival for all evaluable cases

AC•DMP; $P<0.01$), pneumonia (28% vs 15%, $P<0.05$), ileus (11% vs 3.5%, $P<0.05$), and renal failure (10% vs 2.8%, $P<0.05$) were observed among the patients receiving BH-AC•AMP.

Discussion

In Europe and the United States, CR rates of 60%–80% are reportedly achieved by DNR, ara-C, and 6-thioguanine combination chemotherapy (DAT or TAD) for adult AML patients [4]. In Japan, 6-thioguanine (6TG) is not commercially available for clinical use, and 6MP is commonly used in its place. BH-AC is often used in Japan in place of ara-C in the treatment of AML, as it has been shown to exhibit a similar antileukemic effect with relatively little treatment-schedule dependency [11]. Several trials have revealed that the combination of DNR, BH-AC, 6MP, and PSL (BH-AC•DMP) produces clinical effects identical to those of TAD or DAT [20].

ACR has reportedly exerted a greater inhibitory effect on RNA synthesis and less cardiotoxicity than DNR and doxorubicin in preclinical studies and has produced CR rates of 18%–43% for AML patients in phase II studies [3, 12, 14, 15, 22, 24, 27]. The dosage employed in these clinical studies varied from a 10-day course of 15 mg/m^2 to 100 or 120 mg/m^2 given for 3 days [14, 15, 22, 27]. In Japan, a daily dose of 0.33–0.7 mg/kg or 20 mg/body for 7–14 days has been used in most studies since 1979, when the first CR was achieved in one AML patient refractory to DNR and ara-C using a daily dose of 20 mg ACR for 20 days [12, 23, 24]. In studies with a relatively small number of patients, combination therapy consisting of a daily dose of 20 mg/body or 14 mg/m^2 ACR with BH-AC, 6MP, and PSL have produced chemotherapeutic effects similar to those of BH-AC•DMP [7, 8]. In the present study a similar ACR schedule was adopted, and the ACR and DNR schedules were therefore quite different. A comparison between the results obtained for the two arms is nevertheless valid, as the delivered doses of BH-AC, 6MP, and PSL were al-

most the same in both arms and no difference was observed between the two arms in hematological findings at the termination of the first course.

In the present study, BH-AC•DMP and BH-AC•AMP showed no statistically significant difference in CR rates or DFS within M1, M2, M4, or M5 subtype cases (FAB classification). The CR rate obtained with BH-AC•AMP for these four FAB subtypes in the present study (56.8%) seems somewhat low in comparison with the CR rates of 68%–77% that have been obtained in other studies with a small number of AML patients using similar protocols of 12-20 mg/m^2 ACR given for 7 days with ara-C [7, 13, 15]. In a national study in Denmark comparing 75 mg/m^2 ACR given for 3 days versus 45 mg/m^2 DNR given for 3 days concomitantly with a continuous 7-day infusion of ara-C at 100 mg/m^2 daily, the authors reportedly obtained a significantly higher CR rate (66% vs 50%) in favor of the regimen with ACR [6]. In the present study, although we observed an equivalency between ACR and DNR in the achievement of a CR for M1, M2, M4, and M5 subtypes, the results failed to show any similar superiority of ACR over DNR and thus suggest that a higher dose of ACR given over a short period may provide better chemotherapeutic effects than a relatively small dose given for 10–14 days.

For the subtype M3, the CR rate obtained with BH-AC•AMP was significantly lower than that attained with BH-AC•DMP. The reason for this difference is not yet clear. Reports on the phase II trials of ACR for the most part have not rigorously distinguished AML subtypes and therefore have provided little information on its effect on the M3 subtype [3, 12, 14, 15, 22, 24, 27]. The results of studies on ACR-containing combination chemotherapy, in which high CR rates for M3 were observed in very limited numbers [7, 19], were also not very informative about its effect on the M3 subtype [13, 15]. In the Danish national study, no difference in the clinical effects of the ACR plus ara-C regimen on the various FAB subtypes was reported [6]. In the present study, the median total dose of ACR given to M3 patients (287 mg; range, 200–400 mg) was lower than that of DNR (355 mg; range, 80–630 mg), and this may be the reason why the CR rate among M3 patients was lower for ACR than for DNR. Further study is necessary to determine the optimal ACR dose in combination therapy for M3.

Although the two induction therapy regimens of the present study produced almost the same ratio of long-term survivors to treated cases, the survival curve for the first 1 or 2 years appears to have been somewhat better for BH-AC•DMP than for BH-AC•AMP as reflected in the P values of 0.0091 (GW) and 0.196 (LR). This early difference would seem to be the result of a lower remission rate and a poorer prognosis for nonresponders in the BH-AC•AMP regimen. In DFS values, there was no significant difference between the two arms. The probability of long-term survival among CR cases appears to be unrelated to whether a CR was attained with BH-AC•DMP or with BH-AC•AMP.

As to the adverse effects encountered during the induction period, higher frequencies of diarrhea, ileus, pneumonia, and renal failure were observed for BH-AC•AMP than for BH-AC•DMP. Reports on the phase II trials of ACR indicate that it has caused nausea or vomiting in 33%–86% of patients and diarrhea in 15%–42% of patients [3, 14, 15, 22, 27]. Japanese reports have also noted high frequencies of diarrhea and hematuria with BH-AC•AMP regimens similar to those of the present study [9, 25]. It thus appears that the combined administration of ACR with BH-AC and 6MP, as in the present study, increases the frequency of diarrhea and ileus symptoms. As pneumonia and renal failure may reasonably be considered to be complications rather than adverse effects, the higher frequencies noted during BH-AC•AMP treatment may be attributable to the larger number of patient failures in that arm.

We observed no difference in the frequency of clinical cardiotoxicity between the two arms. In the above-cited Danish trial involving a larger ACR dose, on the other hand, it was noted that cardiac symptoms (WHO grades 4–5) occurred more frequently with ACR (4%) than with DNR (0) when each was used in combination with ara-C and 6TG [6]. Using 100 mg/m^2 ACR daily for 3 days along with ara-C daily for 7 days, Montastruc et al. [16] also observed 3 cases complicated by severe cardiac toxicity among 94 elderly AML patients. Both studies thus suggest that daily doses of ACR larger than those delivered in our study may involve a risk of cardiac problems.

In summary, the results of the present study, at least on the basis of the long-term outcome, indicate that the drug combination BH-AC•AMP is similar in effectiveness to BH-AC•DMP chemotherapy for types M1, M2, M4, and M5 of adult AML. Furthermore, the results indicate that the optimal dose of ACR in the treatment of the M3 subtype warrants further study and that elucidation of the optimal employment of ACR and DNR in adult AML may also be of value for further clinical improvement in this disease.

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Appendix

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