(26) Ishikawa M, Dennis JW, Man S, et al: Isolation and characterization of spontaneous wheat germ agglutinin-resistant human melanoma mutants displaying remarkably different metastatic profiles in nude mice. Cancer Res 48:665-670, 1988
(27) Ishikawa M, Fernandez B, Kerbel RS: Highly pigmented human melanoma variant which metastasizes widely in nude mice, including to skin and brain. Cancer Res 48:4897-4903, 1988
(28) Yagel S, Parhar RS, Jeffrey JJ, et al: Normal non-metastatic human trophoblast cells share in vitro invasive properties of malignant cells. J Cell Physiol 136:455-462, 1988
(29) Khokha R, Denhardt DT: On the use of anti-sense RNA: Down-regulation of mRNA encoding a metalloproteinase inhibitor. Anticancer Res 7:653-660, 1987
(30) Khokha R, Waterhouse P, Yagel S, et al: Modulation of the collagenase inhibition (TIMP) mRNA levels by anti-sense RNA influences the invasiveness of mouse 3T3 cells. J Cell Biochem 12B:307, 1988
(31) Carmichael DF, Sommer A, Thompson RC, et al: Primary structure and cDNA cloning of human fibroblast collagenase inhibitor. Proc Natl Acad Sci USA 83:2407-2411, 1986
(32) Khokha R, Waterhouse P, Yagel S, et al: Antisense RNA-induced reduction in murine TIMP levels confers oncogenicity on murine 3T3 cells. Science 243:947-952, 1989
(33) Barner M, Mayer M, Schirrmacher V, et al: Involvement of both heparanase and plasminogen activator in lymphoma cell mediated degradation of heparin sulfate in subendothelial extracellular matrix. J Cell Physiol 128:209-306, 1986
(34) Nicolson GL, Winkelhake JL: Organ specificity of blood-borne metastases as determined by cell adhesion. Nature 255:230-232, 1975
(35) Murray JC, Liotta LA, Rennard SI, et al: Adhesion characteristics of murine metastatic and non-metastatic tumor cells in vitro. Cancer Res 40:347-351, 1988
(36) Reich R, Thompson EW, Iwamoto Y, et al: Effects of inhibitors of plasminogen activator, serine proteinases, and collagenase IV on the invasion of basement membranes by metastatic cells. Cancer Res 48:3307-3312, 1988

Phase I Study of an Anti-Breast Cancer Immunotoxin by Continuous Infusion: Report of a Targeted Toxic Effect Not Predicted by Animal Studies

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260F9 Monoclonal antibody-recombinant ricin A chain, an immunotoxin reactive with ≈50% of breast carcinomas, was given by continuous iv infusion at a dose of 50 μg/kg per day or 100 μg/kg per day. Five patients with refractory breast cancer received treatment for from 6 to 8 days. Severe toxic effects, including marked fluid overload and debilitating sensorimotor neuropathies, occurred in most patients. Immunoperoxidase studies suggested that 260F9 monoclonal antibody targeting of the Schwann cells may have induced demyelination and subsequent neuropathy. This is the first report of a targeted toxic effect due to an immunoconjugate. [J Natl Cancer Inst 81:775-781, 1989]

Immunotoxins are a class of biological agents that have recently been used as cancer therapy in phase I trials. Immunotoxins consist of two components: a carrier protein, usually a monoclonal antibody (MAb), and a cytotoxic agent such as ricin toxin A chain (RTA), diphtheria toxin, or *Pseudomonas* exotoxin. Ideally, the toxin is transported to the tumor cell surface by the antibody, which has specificity for a tumor antigen. Once bound to the cell surface, the complex is internalized, the toxin escapes to the cytosol, and toxin-mediated inhibition of protein synthesis occurs. Several reviews detailing immunotoxin cytotoxicity have recently been published (*1,2*).

Animal studies have demonstrated several problems that limit the efficacy of immunotoxins, particularly native RTA conjugates. These problems include rapid clearance by the liver (*3*), the generation of anti-immunotoxin antibodies (*4*), and poor tumor penetration (*5*). Rapid immunotoxin clearance is caused in part by the Kupffer cells, which bind the mannose moieties of native RTA. Although chemical deglycosylation does not eliminate hepatic uptake, Blakey et al. (*6*) have shown in mice that serum levels of the partially deglycosylated RTA immunotoxins are sustained at higher levels than those formulated with native RTA. Recently, recombinant RTA, which is not glycosylated but still has the same potency as the native molecule, has become available. Because recombinant ricin A chain (rRA) lacks carbohydrate

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groups, it also has the theoretical advantage of being less immunogenic than the native protein. When the processes that inactivate the immunotoxin are minimized, higher and more sustained immunotoxin levels should be achieved and better tumor penetration may become possible.

The limited experience with immunotoxins in humans has been exclusively with native RTA containing immunotoxins that have been administered by bolus infusions (*7-9*). Toxic effects seen in these studies in animal models have been largely predictable, and have consisted of fever, malaise, fluid retention, myalgias, hypoalbuminemia, electrocardiogram changes, and hepatitis. All the toxic effects resolved when therapy was discontinued. Unfortunately, clinical responses have been uncommon, with a complete response occurring in only two of 30 patients reported in the literature (*7,9*). In our study of patients with breast cancer, we report the first human use of an immunotoxin that contains rRA and the first study that uses continuous-infusion therapy. In addition, we also report the occurrence of a unique, posttherapy toxic effect that was not predicted by primate trials.

Patients and Methods

Patients

Five patients with biopsy-proven metastatic breast carcinomas that were refractory to standard therapies were selected for treatment. A summary of patient characteristics, including sites of tumor involvement, hormonal receptors, and prior therapies is found in table 1. No patient received treatment for at least 1 month prior to the start of immunotoxin therapy. All had a Karnofsky performance status of ≥80% and a life expectancy of >3 months. There was no evidence of cardiac, hepatic, renal, or neurologic dysfunction, nor were there any signs of an active infection. No patient had any major laboratory abnormalities.

Immunotoxin Preparation

The IgG_1 murine MAb 260F9, rRA, and the 260F9 MAb-rRA were produced by the Cetus Corporation, Emeryville, CA. A series of MAbs directed against breast cancer cell lines and breast carcinoma extracts were produced by standard hybridoma techniques (*10*). The 260F9 MAb was chosen because of its affinity for ≈50% of the breast cancer cell lines and for its limited cross-reactivity with normal tissues (*11*). Genetic engineering techniques were used to manufacture sufficient quantities of pure, unglycosylated RTA. By using 2-iminothiolane, we introduced sulfhydryl groups onto the MAb (*12*). The derivatized antibody was treated with DTNB [5,5′-dithio-*bis*-(2-nitrobenzoic acid)] and mixed with the rRa, which resulted in coupling of the molecules by a disulfide bond. The preparation was processed by size exclusion and affinity chromatography to remove the small amounts of free antibody and RTA. Clinical lots of 260F9 MAb-rRA were prepared and tested for sterility, rabbit pyrogenicity, and murine virus contamination and found to be acceptable.

Protocol

All patients were treated in the Clinical Research Unit at Duke University Medical Center from June 1987 through August 1987. After we obtained informed consent, four patients received a single, 8-day course of treatment. The only exception to this schedule was patient 5, who received 6 days of therapy. The immunoconjugate was diluted in 50 mL of 5% human serum albumin and administered by continuous infusion through a central venous catheter. Patients 1, 2, and 3 received 50 μg of immunotoxin/kg per day for total daily doses of 2.8, 3.0, and 3.02 mg, respectively. Patient 4 and patient 5 received 100 μg of immunotoxin/kg per day for total daily doses of 7.5 and 6.8 mg, respectively. Following completion of treatment, the patients were monitored in the hospital for an additional 48 hours. Two patients had biopsy specimens of chest wall tumors done 48 hours after completing therapy to obtain tissue for immunotoxin penetration analyses. After treatment, the patients were followed regularly at Duke for 3 months; thereafter, they were followed by contact through their community physicians.

All patients were monitored closely for side effects by daily physical examinations, frequent vital signs, daily weights, and daily fluid balances. Also, serial measurements were made of the cbc, electrolyte, creatinine, BUN, total protein, albumin, triglyceride, cholesterol, calcium, and liver profile. Chest

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Table 1. Patient characteristics

Patient No.	Age (yr)	Estrogen receptor/ progesterone receptor*	Previous treatment†	Sites of disease
1	69	−/−	CMF, tamoxifen, C.W. XRT	Chest wall, lungs
2	57	−/−	CMF, doxorubicin, mitomycin, vinblastine, tamoxifen, C.W. XRT	Chest wall
3	77	−/−	CAF, tamoxifen, C.W. XRT	Right pleural disease, liver, cervical nodes
4	43	−/−	CAF, ABMT, tamoxifen, C.W. XRT	Chest wall, lungs
5	55	−/−	CMFVP, megestrol, doxorubicin	Chest wall, lungs, supraclavicular nodes

*− = absence of receptor.
†C = cyclophosphamide; M = methotrexate; F = 5-fluorouracil; C.W. XRT = chest wall radiation therapy; A = doxorubicin; ABMT = autologous bone marrow transplantation; V = vincristine; P = prednisone.

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x rays, electrocardiograms, and chest and abdominal computer tomography scans were performed prior to study, as needed during study, and within 1 month after the completion of therapy.

Blood samples were obtained for pharmacokinetic studies, anti-rRA antibody levels, and anti-260F9 MAb levels. The samples were drawn contralateral to the infusion site prior to infusion, daily, and 0.5, 1, 2, 2.5, 4, 6, 12, and 18 hours after the start of the infusion and on the final day of therapy. Additionally, blood was drawn at 32 and 48 hours and from 14 to 32 days posttreatment. The blood samples were centrifuged within 2 hours of collection, the serum was removed, and the samples were stored at −70 °C.

Pharmacokinetics

Serum levels of 260F9 MAb–rRA were measured by an immunoradiometric assay. First, polyvinylchloride wells of a microtiter plate were incubated overnight with purified rabbit anti-RTA [10 μg/mL in phosphate-buffered saline (PBS)]. The wells were then washed three times with PBS and blocked for 1 hour with heat-inactivated fetal calf serum. Afterwards, patient sera, diluted 1:10 in PBS, were added to the wells. Various concentrations of the immunotoxin for use in formulating a standard curve were diluted in normal serum and added to the wells. All samples were tested in triplicate, and the plate was incubated for 2 hours. After another washing with PBS, a solution of ^{125}I-sheep $F(ab')_2$ anti-mouse immunoglobulin (DuPont, Wilmington, DE) in PBS with 2.5% heat-inactivated fetal calf serum was added to each well and incubated. The solution was formulated so that 3×10^6 cpm were added to each well. After 1 hour and a final washing, the wells were counted in a Packard Autogamma 5780 with the window settings for ^{125}I. Nonspecifically bound radioactivity was determined from the control sera and subtracted before the immunotoxin concentrations were extrapolated from the standard curve.

Anti-Murine and Anti-rRA Levels

The polyvinylchloride wells of a microtiter plate were incubated overnight with either rRA or 260F9 MAb (both in 10 μg of PBS/mL). The plate was washed with PBS and blocked for 1 hour with heat-inactivated fetal calf serum. Patient samples, diluted 1:10 in PBS, and various standard solutions of either anti-murine 260F9 MAb or anti-rRA antibodies (Cetus Corp.) were added in triplicate to each well. Following incubation for 2 hours, the wells were washed and then either ^{125}I-260F9 MAb or ^{125}I-rRA in PBS with 2.5% heat-inactivated fetal calf serum, adjusted to 5×10^6 cpm per well, was added to each well. After 1 hour, the wells were washed again and counted in a Packard Autogamma 5780. Nonspecifically bound radioactivity was determined from pretreatment sera and subtracted before concentrations of the antibodies were extrapolated from the standard curves. 260F9 MAb and rRA were iodinated as described by Fraker and Speck (*13*).

Immunoperoxidase Studies

Immunoperoxidase studies were performed on acetone-fixed frozen sections of tumor biopsy specimens and nerves, using the avidin–biotin peroxidase complex (ABC) procedure as described (*14*). To determine 260F9 antigen expression, we tested serial dilutions of 260F9 MAb against known positive breast carcinomas, and found the optimal concentration of antibody to be 25 μg/mL. We used irrelevant murine IgG_1 at 25 μg/mL as a negative control.

To determine if immunotoxin administered to patients had bound to the target, we used a modification of the ABC procedure. To detect bound mouse immunoglobulin, we incubated tissues from the patients with biotinylated horse anti-mouse immunoglobulin, followed by the avidin and biotinylated horseradish peroxidase complex. To detect bound ricin, we incubated tissue sections with rabbit anti-RTA followed by biotin-conjugated goat anti-rabbit immunoglobulin and ABC. Prior to testing the patient specimens, we determined optimal dilutions of each reagent in a checkerboard fashion with known 260F9 antigen-positive breast tumor sections that had been preincubated in vitro with immunotoxin.

Results

Patient Toxic Effects

Four patients completed 8 days of the infusion, and patient 5 requested that treatment be discontinued on day 6 because of side effects. The 260F9 MAb–rRA shared many adverse effects observed with other immunotoxins (table 2). All the patients suffered fevers >38.4 °C, anorexia, malaise, arthralgias, and myalgias. Nausea and diarrhea were transient problems for only one patient. Another patient developed evidence of a drug reaction on day 6 when she developed an erythematous-vesicular rash on her hands, finger arthritis, and a 7% eosinophilia. All the aforementioned side effects resolved when therapy was stopped.

Fluid retention and peripheral edema were problems common to all patients with maximal weight gains of 1–5 kg occurring on day 8. Although several patients complained of dyspnea, none had chest x-ray evidence of congestive heart failure. Moderate-dose diuretics (Lasix, 60 mg) failed to reverse the fluid retention, but the fluid gain did resolve in three patients when the immunotoxin was stopped. The other two patients required hospitalization 5 and 7 days after immunotoxin treatment for pulmonary edema and symptomatic peripheral edema that was unassociated with acute cardiac diseases. The fluid overload of these two patients responded quickly and completely to moderate-dose diuretics, and they had no further volume problems.

Table 2. Side effects of 260F9 MAb-rRA infusion

Symptoms	No. of patients	Range
Fever	5	>38 °C
Weight gain/edema	5	1.0-5.0 kg
Arthralgias/myalgias	5	—
Dyspnea on exertion	3	—
Finger arthritis	1	—
Rash	1	—
Hypotension	1	Systolic blood pressure <90 mm Hg
Nausea and diarrhea	1	—

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Patient 4, who had advanced pulmonary disease prior to therapy, died during the initial hospitalization. On day 3, she developed a temperature of 39.5 °C and hypotension. Two days later, coagulase negative staphylococcus was grown from her blood. Despite appropriate antibiotics, she developed progressive pulmonary air space disease. On day 8 coagulase-negative staphylococcus was again grown, and the central catheter was removed. Later that day she required intubation; a Swan-Ganz catheter showed low central venous pressures that were compatible with sepsis and adult respiratory distress syndrome. Although subsequent cultures were negative, the patient died of progressive pulmonary and cardiovascular failure on day 23.

Several laboratory abnormalities developed in each patient during the course of the infusion (table 3). Two notable abnormalities were the falls in the serum albumin and serum sodium that paralleled the fluid retention. The sodium levels fell as low as 126 meq/L and 120 meq/L in two patients, although neither patient manifested mental status changes. No proteinuria was found to explain the hypoalbuminema; urine sodium studies were not done. Minor elevations of the liver transaminases, serum glucose, and serum triglycerides also developed in several patients. All the abnormal laboratory values returned to normal within 72 hours of completion of the infusions.

Debilitating plexopathies and neuropathies occurred in three patients, two at the 50-μg/kg per day dose and one at the 100-μg/kg per day dose. The neurologic symptoms began as a plexopathy on the side of previous chest wall irradiation about 2 weeks after the completion of the infusion. Over the ensuing 2 weeks, the patients developed typical sensorimotor neuropathies of the other three extremities. The diagnoses were confirmed by neurologic examinations and nerve conduction studies in the three cases. Two of the three patients had normal brain and spinal cord examinations by computer tomography scans. The neuropathies were most severe at 2–3 months after treatment and resulted in a decline in Karnofsky status from 80% (normal activity with effort) to 40% (incapable of self care). During the following 6 months, the patients had complete recovery of their motor function, but they continued to suffer from paresthesias of their hands and feet.

Tumor Response

The clinical responses were followed by appropriate radiologic studies and by serial measurements of chest wall lesions in four patients and serial measurements of liver lesions in the fifth patient. There were no findings suggestive of tumor stabilization, tumor regression, a mixed response, or symptomatic improvement in any patient. Three patients died within 9 months following treatment, and a fourth patient has progressive disease 1 year later.

Table 3. Major laboratory abnormalities associated with the 260F9 MAb–rRA immunotoxin

Test	No. of patients	Range
Glucose	5	120–200 mg/L
Triglycerides	5	246–1,244 mg/dL
Sodium	4	120–132 mEq/L
Albumin	4	2.6–3.2 g/dL
SGOT/SGPT	3	80–149/65–73 U/L

Tumor Penetration

Immunoperoxidase analyses were done on biopsy specimens from the chest wall from two patients who were using antibodies against both murine immunoglobulin and RTA. No murine immunoglobulin or RTA, either free or as immunotoxin, could be detected bound to the malignant cells, in the tumor matrices, or in the perivascular spaces. Both biopsy specimens from the chest wall bound 260F9 MAb in vitro.

Nerve Studies

A sural nerve biopsy was done in one patient during the period of profound neuropathic disturbance. The results of this biopsy showed marked axonal loss and segmental demyelination. No inflammatory infiltrates or other abnormalities were found on microscopic examination. The biopsy failed to reveal any bound immunotoxin or 260F9 MAb; however, immunoperoxidase studies showed that the 260F9 antigen was present on the nerve in a distribution consistent with either Schwann cells or myelin (fig. 1). Seven of nine normal human nerves and nerves from two untreated monkeys (one rhesus and one cynomologus) were also found to bind the 260F9 MAb. Irrelevant mouse MAb did not bind in any immunoperoxidase study. The finding of these positive immunochemical results depended on the details of the fixation and drying techniques. Careful attention to these details was maintained for all the immunochemical procedures.

Pharmacokinetics

The 260F9 MAb–rRA serum levels were determined by immunoradiometric assay for the five infusions. The steady-state immunotoxin concentration for the group was reached at 24 hours. Even at similar doses, there was marked interpatient variability of steady-state levels. The steady-state levels ranged between .235 ± .011 μg/mL for patient 1 and .905 ± .020 μg/mL for patient 5. Once steady states were reached, the immunotoxin concentrations remained constant for 6 days in four patients. The steady-state level of patient 2 remained constant for 3 days; afterwards, it dropped by one-third and remained constant until the end of the infusion. Assuming an immunotoxin distribution limited to a 3-L plasma volume, we calculated an immunotoxin half-life between 4 and 6 hours for each patient.

Anti-Immunotoxin Antibodies

The levels of anti-rRa and anti-260F9 MAb antibodies were assayed by an immunoradiometric assay, which does not distinguish between IgG and IgM. The lower limit of sensitivity was 1 μg/mL for the anti-260F9 MAb assay and 5 μg/mL for the anti-rRA assay. Four patients developed anti-rRa antibodies, and three generated anti-260F9 MAb antibodies (table 4). Only patient 4, the patient with sepsis and the most heavily pretreated of the group, did not form antibodies to either component of the immunotoxin.

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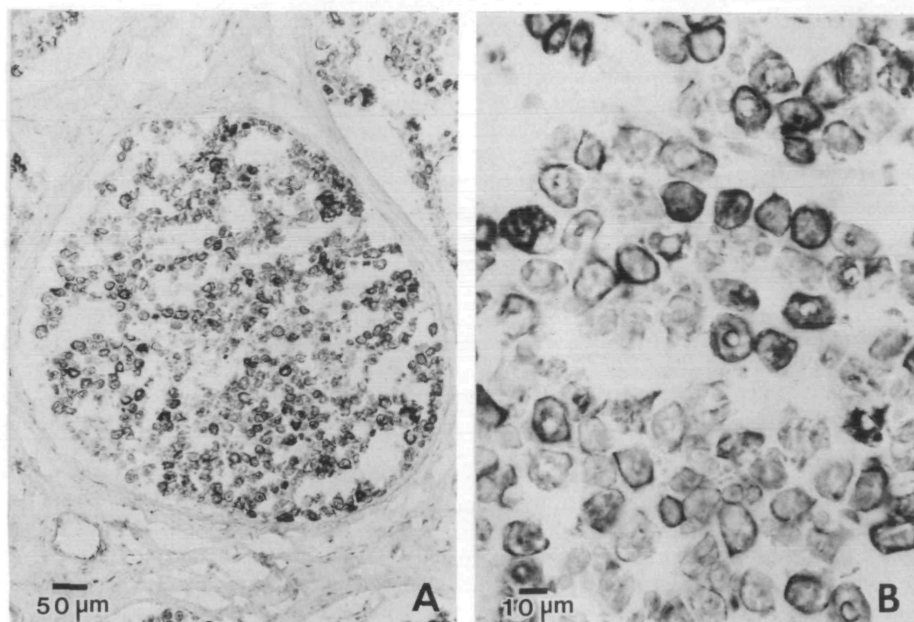

Figure 1. (A) Immunoperoxidase stains show binding of the 260F9 MAb to human nerve. There is distinct surface staining around the periphery of many nerves, which at high power (B) can be seen to have a distribution consistent with either the Schwann cell membrane or the myelin sheath.

Discussion

The protocol was designed for serial dose escalations from 50 µg/kg per day to 450 µg/kg per day. Despite expectations based on animal studies that the immunotoxin would be well tolerated (data on file at the Cetus Corp.), the trial was stopped early because of severe toxic effects. Many of the acute side effects of the 260F9 MAb-rRA were similar to those reported for other immunotoxins and by Weiner et al., who used bolus infusions of the 260F9 MAb-rRA in four patients.[1] The pathophysiology of one of these side effects, hypoalbuminemia, remains an unexplained phenomenon of immunotoxin therapy. None of our patients had proteinuria, severe liver dysfunction, or a protein-losing enteropathy, which would explain the low albumin. Also, the rapid return of the albumin after the immunotoxin was discontinued is not compatible with protein loss caused by dysfunction of a major organ. The association of the fluid retention and hypoalbuminemia is unclear. In our study and the study by Spitler et al. (*7*), fluid retention paralleled the decrease in albumin, unlike protein-losing diseases where hypoalbuminemia precedes the fluid gain. Also, fluid gains of 4 kg and 5 kg occurred in two patients who had only modest drops in their serum albumin to 3.2 mg/dL. While the low albumin may enhance accumulation of fluid, it is unlikely to be the primary cause.

One mechanism that has been proposed to explain the fluid retention and hypoalbuminemia is a capillary leak syndrome. Although the murine immunoglobulin (IgG_1) used to make the 260F9 MAb-rRA does not ordinarily bind to human monocytes, Weiner et al. have submitted evidence showing that the 260F9 MAb-rRA and other RTA-containing immunotoxins bind to the human monocyte Fc receptors.[1] It is possible that monocyte activation or death may lead to the release of mediators that bring about the capillary leakage. Although the pathophysiology of the fluid gain remains unclear, poor diuresis following moderate-dose diuretics during the immunotoxin infusion suggests that the fluid was extravascular.

Two of our patients treated by continuous infusion and one treated by bolus infusions of 260F9 MAb-rRA developed symptomatic fluid overload after discharge, probably because of the intravascular reaccumulation of the fluid. There was no indication by noninvasive studies of cardiac damage by the immunotoxin. Because the patients were elderly or were heavily pretreated with doxorubicin, they were less able to tolerate the rapid fluid shifts and developed symptoms that necessitated hospitalization. Fluid overload following immunotoxin therapy may not have been seen in other stud-

Table 4. Anti-immunotoxin antibody levels (µg/mL)

Patient No.	Anti-260F9 MAb	Anti-rRA
1	100 (24)*	54 (8)
2	31 (18)	49 (8)
3	10 (9)	51 (32)
4	0	0
5	0	71 (9)

*First day detectable.

[1]Weiner LM, O'Dwyer J, Kitson J, et al. A phase I evaluation of the ricin A chain anti-breast carcinoma immunoconjugate 260F9 MAb-rRA; submitted for publication.

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