Safety and Efficacy of Gemtuzumab Ozogamicin in Combination With Chemotherapy for Pediatric Acute Myeloid Leukemia: A Report From The Children's Oncology Group

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ABSTRACT

Purpose

While gemtuzumab ozogamicin (GMTZ) is commonly used in the treatment of acute myeloid leukemia (AML) in combination with standard chemotherapy agents, the pediatric maximum-tolerated dose (MTD) of GMTZ in combination with chemotherapy has not been determined.

Patients and Methods

The Children's Oncology Group AAML00P2 trial sought to define the MTD of GMTZ in combination with cytarabine and mitoxantrone and cytarabine and L-asparaginase chemotherapy regimens.

Results

The MTD for GMTZ in combination with cytarabine and mitoxantrone was 3 mg/m² while the MTD in combination with cytarabine and L-asparaginase was 2 mg/m². Toxicities observed in both treatment regimens were typical of those seen in the relapsed AML setting and consisted primarily of infectious complications. The overall remission response rate (mean $\pm$ SE) was 45% $\pm$ 15% and the 1 year event-free survival and overall survival estimates were 38% $\pm$ 14% and 53% $\pm$ 15%, respectively.

Conclusion

This trial determined the pediatric MTD for GMTZ with two commonly used AML chemotherapy combinations. Based on these results, an ongoing phase III trial conducted within the Children's Oncology Group is evaluating the effect of GMTZ when added to standard AML therapy.

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INTRODUCTION

Although acute myeloid leukemia (AML) occurs less frequently than acute lymphoid leukemia in children, the number of children who suffer a relapse of AML or acute lymphoid leukemia are approximately equal.¹ Unfortunately, despite intensive salvage therapies that include hematopoietic stem-cell transplantation (HSCT), a substantial portion of children with relapsed AML die from refractory disease or treatment-related toxicity. Thus, new therapies are needed both for de novo and relapsed AML.

Current efforts to improve AML outcome have focused on the development of targeted therapies that may allow improved antileukemic effect without substantially increasing toxicity. Of these molecularly targeted therapies, gemtuzumab ozogamicin (GMTZ) is perhaps the most comprehensively studied in adults.^{2,3} GMTZ con-

sists of a humanized anti-CD33 antibody linked to calicheamicin, a highly potent chemotherapeutic. After binding to CD33, GMTZ is internalized, with subsequent hydrolysis releasing calicheamicin that in turn binds the minor groove of DNA and causes double-stranded DNA breaks.

Multiple adult studies have determined the maximum-tolerated dose (MTD) of GMTZ as a single agent and in combination with multiple chemotherapy regimens.^{2,4} A phase I trial determining dose-limiting toxicity of GMTZ as a single agent in children with AML has been reported.⁵ While additional pediatric case series of GMTZ have been reported,⁶ dose-finding studies of GMTZ in chemotherapy combinations in children have not been reported.

The Children's Oncology Group (COG) trial AAML00P2 sought to determine the MTD and provide preliminary response data using GMTZ in

combination with two chemotherapy regimens commonly used in pediatric AML: high-dose cytarabine and mitoxantrone and high-dose cytarabine with L-asparaginase (Capizzi II). This report summarizes the results of the AAML00P2 trial.

PATIENTS AND METHODS

Patients

The AAML00P2 trial enrolled patients with refractory disease after initial induction therapy for de novo AML, an initial remission duration of less than 1 year, or secondary AML without prior therapy. Enrollment criteria included age younger than 21 years at time of study enrollment, adequate cardiac, renal, and hepatic function, no prior history of veno-occlusive disease (VOD), an appropriate performance status, and a 6-month duration between study enrollment and prior SCT. Exclusion criteria included CNS leukemia defined by either no clinical evidence of CNS disease or a negative lumbar puncture, pregnancy, Trisomy-21, Fanconi anemia, and history of clinical VOD. Cytogenetic results were not centrally reviewed.

Initial dose finding was performed in a limited number of institutions. Once the MTD was established for each study arm, the study was opened throughout COG. Planned accrual was 20 assessable patients for each study arm once the MTD was determined.

Signed informed consent was obtained from either study participants or guardians. The trial was approved by local institutional review boards and performed in a manner consistent with tenets of the Declaration of Helsinki and with Good Clinical Practice guidelines.

Treatment Regimens

Patients were nonrandomly assigned to one of two treatment arms in a dose de-escalation study design. The starting dose of GMTZ was 3 mg/m² in both treatment arms with GMTZ dose de-escalation to 2 mg/m² if the initial dose was deemed too toxic. GMTZ dose levels in children younger than 3 years of age were 0.1 mg/kg and 0.07 mg/kg, respectively. Dose determination was performed in arm A followed by arm B. Once the GMTZ dose was defined in both treatment arms, an expanded cohort of patients was enrolled to obtain further regimen-related toxicity and preliminary efficacy estimates. Expanded cohort enrollment began in arm A. Once the arm A expanded cohort was filled, then patients were enrolled onto the arm B expanded cohort.

Arm A contained cytarabine 1,000 mg/m²/dose (33 mg/kg/dose for patients < 3 years of age) as an intravenous (IV) infusion over 2 hours every 12 hours, on days 1 through 4, for a total of eight doses (8 g/m² or 264 mg/kg for patients < 3 years of age) and mitoxantrone 12 mg/m²/dose (0.4 mg/kg/dose for patients < 3 years of age) as an IV infusion over 1 hour on days 3 through 6 for a total of four doses (48 mg/m² or 1.6 mg/kg for patients < 3 years of age). GTMZ was given as an IV infusion over 2 hours on day 7.

Arm B used cytarabine 3,000 mg/m²/dose (100 mg/kg/dose for patients < 3 years of age) as an IV infusion over 3 hours every 12 hours, on days 1 and 2, for a total of four doses (12 g/m² or 400 mg/kg for patients < 3 years of age) and L-asparaginase 6,000 U/m² intramuscularly (IM) on day 2, hour 18 (for patients < 3 years of age, 200 U/kg IM). GMTZ was given as an IV infusion over 2 hours on day 3. Cytarabine 3,000 mg/m²/dose (100 mg/kg/dose for patients < 3 years of age) was given as an IV infusion over 3 hours every 12 hours, on days 8 and 9, for a total of four doses (12 g/m² or 400 mg/kg for patients < 3 years of age) and L-asparaginase 6,000 U/m² IM on day 9, hour 18 (for patients < 3 years of age, 200 U/kg IM).

Intrathecal therapy was not given on either study arm. Poststudy treatment was at the discretion of the treating physician.

Safety Assessments

The primary safety assessment was the monitoring and reporting of National Cancer Institute Common Toxicity Criteria version 2 toxicities and any grade of VOD both during protocol therapy and subsequent HSCT. VOD grading was based on serum bilirubin level, weight gain, and level of clinical intervention required (VOD grading scale appears in online-only Appendix). All enrolled patients who received GTMZ were monitored for toxicity

throughout protocol therapy. Patients who received HSCT were also evaluated at day 100 post-transplantation for VOD. The MTD was defined as the dose level immediately below the dose level at which two or more patients of a cohort, consisting of three to six patients, experienced dose-limiting toxicity. Toxicity grades of 3 and 4 were considered dose limiting with the exception of grade 3 or 4 hyperbilirubinemia, ALT elevation, or AST elevation lasting fewer than 7 days, grade 3 or 4 nausea, emesis, fever/infection, bleeding, and disseminated intravascular coagulation. Hematologic dose-limiting toxicity was defined as failure to recover peripheral absolute neutrophil count (ANC) more than 500/mL and platelets more than 20,000/mL within 56 days of initial treatment and the absence of recurrent or persistent leukemia. VOD assessment was based on the criteria of McDonald et al⁷; grade 2 VOD was considered dose limiting.

Efficacy Assessments

Attainment of complete remission (CR) was the primary efficacy end point. Patients were assessed for remission status after one course of protocol therapy. A CR was defined as an M1 bone marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with recovery of the ANC to greater than 1,000/ μ L and a platelet count greater than 100,000/ μ L. Responses which met bone marrow response and ANC criteria, but did not have a platelet count of greater than 100,000/ μ L, were classified as complete response without platelet recovery, provided that they did not require platelet transfusions within 7 days of response evaluation. Patients with an increase in bone marrow blasts by $\geq$ 20% or development of extramedullary disease were classified as having progressive disease (PD). All other patients were classified as stable disease (SD).

Statistics

Data were analyzed through March 9, 2007. Observed differences in proportions were tested using the χ^2 test and Fisher's exact test when data were sparse. The Kaplan-Meier method was used to calculate estimates of overall survival (OS) and event-free survival (EFS).⁸ OS and EFS estimates are reported with their Greenwood SEs.⁹ OS is defined as time from study entry to death from any cause. EFS was defined as time from study entry to PD at the end of the course, relapse, or death from any cause. Children lost to follow-up were censored at their date of last known contact or at a cutoff 6 months before March 9, 2007 in order to compensate for the tendency of deaths and relapses being reported sooner than ongoing follow-up. Two patients who were deemed ineligible after completion of protocol therapy were not included in the analyses.

RESULTS

Patient Characteristics

AAML00P2 patient characteristics are found in Table 1. Patient characteristics were typical for patients with relapsed, refractory, or secondary AML. Significant differences in sex, age, ethnicity, disease type, and presentation WBC were not observed. However, eight patients with primary induction failure were enrolled onto arm B while only one patient with refractory disease was enrolled onto arm A. This difference was statistically significant ($P = .027$). Data on two arm B patients who were enrolled but unassessable for response are also included in Table 1. Two patients were deemed ineligible; one patient was noted not to meet eligibility criteria on data review and the other patient did not have appropriate documentation of informed consent.

MTD Determination

The starting GMTZ dose of 3 mg/m² was well tolerated in the first three patients enrolled onto the cytarabine and mitoxantrone study arm (arm A) and was set as the MTD for this study arm. In the high-dose cytarabine and L-asparaginase arm (arm B), all three patients treated with GMTZ at 3 mg/m² had dose-limiting toxicities.

Table 1. Patient Characteristics

Characteristic	All Patients		Arm A (3 mg/m ²)		Arm B (2 mg/m ²)		Arm B (3 mg/m ²)	
	No.	%	No.	%	No.	%	No.	%
Total	45		20	44	22	49	3	7
Sex								
Male	28	62	14	70	13	59	1	33
Female	17	38	6	30	9	41	2	67
Age, years								
Median	11.5		12.8		10.8		10.6	
Range	0.8-19.8		1.2-19.3		2.1-19.8		0.8-16.1	
0 to < 2	2	4	1	5	0	0	1	33
2 to < 10	17	38	7	35	10	45	0	0
10-21	26	58	12	60	12	55	2	67
Race								
White	30	67	11	55	18	82	1	33
Black	6	13	4	20	2	9	0	0
Asian	1	2	1	5	0	0	0	0
Other	5	11	2	10	2	9	1	33
Unknown	3	7	2	10	0	0	1	33
Ethnicity								
Non-Spanish, non-Hispanic	37	82	16	80	19	86	2	67
Spanish or Hispanic	7	16	4	20	3	14	0	0
Unknown	1	2	0	0	0	0	1	33
Prior HSCT received								
Yes	3	7	1	5	0	0	2	67
No	42	93	19	95	22	100	1	33
Disease type								
Acute myeloid leukemia induction failure	9	20	1	5	7	32	1	33
Acute myeloid leukemia early relapse	23	51	13	65	8	36	2	67
Myelodysplastic syndrome	1	2	0	0	1	5	0	0
Acute myeloid leukemia as a second malignant neoplasm	12	27	6	30	6	27	0	0
Total	45		20		22		3	
WBC								
Median	5.0		7.0		4.0		6.0	
Range	1-268		1-193		1-169		4-268	
Cytogenetics								
Normal	7	23	2	17	5	31	0	0
Good risk	2	7	1	8	1	6	0	0
Intermediate risk	17	57	7	58	8	50	1	100
Poor risk	3	10	2	17	1	6	0	0
Failed	1	3	0	0	1	6	0	0

Abbreviation: HSCT, hematopoietic stem-cell transplantation.

Patient 1 experienced grade 3 pharyngitis and transaminitis; patient 2 experienced grade 4 pancreatitis; and patient 3 had grade 3 transaminitis and grade 2 hyperbilirubinemia concurrent with fatal *Pseudomonas* sepsis. Because of these dose-limiting toxicities, the GMTZ dose was de-escalated to 2 mg/m² in arm B and a total of six patients were treated at this dose level. Of these six patients, one had grade 4 pancreatitis with a grade 3 infection, two additional patients had grade 3 infections, and three patients had minimal nonhematologic toxicities. Thus, the MTD of GMTZ was set at 2 mg/m² in combination with high-dose cytarabine and L-asparaginase using the Capizzi II regimen schedule.

Toxicity Data

Toxicity data are summarized in online-only Table A1. Notably, approximately 75% of patients in both treatment arms had at least one grade 3 or 4 nonhematologic toxicity reported. Infectious complica-

tions were most common, with infection with neutropenia experienced by 40% of patients on arm A and 50% of patients on arm B. Two patients treated on arm B with high-dose cytarabine and GMTZ experienced severe pancreatitis. One of these patients received GMTZ at 3 mg/m², and the second received GMTZ at 2 mg/m². The observed pancreatitis rate for arm B was 8% (95% CI, 0.98% to 26.0%). Other reported toxicities were typical of toxicities seen in patients undergoing AML induction therapy (Appendix Table A1, online only).

Six patients died while on protocol or within 30 days of termination of protocol therapy. Two patients died from sepsis with *Pseudomonas* and *Pseudomonas/Acinetobacter* sepsis, respectively. One patient on arm A died with presumed culture negative sepsis with an acute drop in cardiac shortening fraction to 14% approximately 17 days after receiving GMTZ. One patient died from toxicity during salvage chemotherapy for the treatment of PD after completing AAML00P2 protocol specified therapy. Two patients died of PD.

One patient, who received a matched-related donor SCT 229 days before AAML00P2 therapy, developed VOD on arm B at a GMTZ dose of 3 mg/m². Concurrent with VOD, the patient experienced grade 4 pancreatitis and recovered with supportive care measures alone. Four of 28 patients developed VOD during HSCT with two patients having grade 1 and one patient each with grades 3 and 4. The interval to HSCT was fewer than 3 months in the patient with grade 4 VOD. All four patients with VOD recovered with only the patient with grade 4 VOD receiving defibrotide.

Twelve of 28 patients died after SCT. Of these, four died from transplant-related toxicity. Reported causes of death were acute respiratory distress syndrome, multisystem organ failure, and infection. Transplant-related mortality was not associated with AAML00P2 treatment arm.

Response Data

Induction response data are presented in Table 2. Approximately 55% of patients with either AML or myelodysplastic syndrome on arm A achieved either a complete response or complete response without platelet recovery while 40% of patients on arm B (GMTZ dose 2 mg/m²) did so. This difference was not statistically significant. Thirty-five percent of patients had SD on arm A while 45% of patients had SD on arm B.

The median follow-up for all patients alive at last contact was 642 days (range, 192 to 1,190). The median for arm A patients is 703 days (range, 192 to 1,190) and for arm B 2 mg/m² patients is 422 days (range, 288 to 597). Figure 1 illustrates EFS and OS for the overall trial; 2-year EFS and OS estimates are 31% ± 15% and 45% ± 16%, respectively. EFS and OS estimates at 1 year by study arm are reported in Table 3. These results parallel the remission induction results with

Fig 1. AAML00P2: all 45 eligible patients by event-free survival (EFS) and overall survival (OS) from study entry.

an increased survival in arm A patients. However, the survival differences are not statistically significantly different. Moreover, Table 3 also reports EFS and OS by initial diagnosis (induction failure, relapsed AML, or secondary AML), demonstrating the different proportions and outcomes among these patient subgroups.

DISCUSSION

This study has defined the pediatric MTD of GMTZ to be 3 mg/m² in combination with cytarabine and mitoxantrone and 2 mg/m²

Table 2. Treatment Response at End of Course 1

Patient Group	All Patients		Arm A (3 mg/m ²)		Arm B (2 mg/m ²)		Arm B (3 mg/m ²)	
	No.	%	No.	%	No.	%	No.	%
All								
CR	15	35	7	35	7	35	1	33
CRp	5	12	4	20	1	5	0	0
SD	16	37	7	35	9	45	0	0
PD	4	9	1	5	2	10	1	33
Death	3	7	1	5	1	5	1	33
Unassessable	2		0		2		0	
AML/MDS								
CR	10	31	5	36	4	27	1	33
CRp	3	9	2	14	1	7	0	0
SD	13	41	6	43	7	47	0	0
PD	3	9	0	0	2	13	1	33
Death	3	9	1	7	1	7	1	33
Unassessable	1		0		1		0	
Secondary AML								
CR	4	36	2	33	3	60	0	0
CRp	2	18	2	3	0	0	0	0
SD	4	36	1	17	2	40	0	0
PD	1	9	1	17	0	0	0	0
Death	0	0	0	0	0	0	0	0
Unassessable	1		0		1		0	

Abbreviations: CR, complete response; CRp, complete response without platelet recovery; SD, stable disease; PD, progressive disease; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Table 3. Event Free and Overall Survival at 1 Year

Arm	No. of Patients	EFS at 1 Year (%)	95% CI	OS at 1 Year (%)	95% CI
A, 3 mg/m ²					
Overall	20	55.0	32.8 to 77.2	64.6	43.1 to 86.2
Induction failure	1	100	—	100	—
Relapsed AML	13	46.2	18.5 to 73.8	60.6	32.9 to 88.2
Secondary AML	6	66.7	28.2 to 100	66.7	28.2 to 100
B, 2 mg/m ²					
Overall	22	21.8	3.8 to 39.9	45.0	23.6 to 66.4
Induction failure	7	25.0	0 to 55.6	46.9	9.6 to 84.2
Relapsed AML	8	12.5	0 to 35.9	25.0	0 to 55.6
Secondary AML	6	33.3	0 to 71.8	66.7	28.2 to 100

Abbreviations: EFS, event-free survival; OS, overall survival; AML, acute myeloid leukemia.

in combination with cytarabine and L-asparaginase. Moreover, the toxicities of GMTZ combined with chemotherapy did not appear substantially different from standard relapsed AML reinduction regimens.^{10,11}

As expected in the relapsed AML setting, infectious complications were most prominent.¹² The overall rate of infectious complications did not appear to differ substantially from other reported AML treatment regimens. Thus, the addition of GMTZ to standard AML chemotherapy does not appear to increase the risk of infectious complications. Notably, the two patients who died of culture-proven sepsis both received protocol therapy on an outpatient basis. While the utility and cost-effectiveness of mandated hospitalization until neutrophil recovery is controversial, this experience provides at least anecdotal evidence supporting hospitalization until neutrophil recovery in patients with high-risk AML.

The occurrence of pancreatitis in two patients treated on arm B therapy was unexpected. However, additional data from ongoing trials is needed to determine whether the observed pancreatitis rate is higher than that seen with the Capizzi high-dose cytarabine and L-asparaginase regimen alone.

Although a substantial concern before study opening, VOD was not a clinically important observed toxicity for patients during protocol therapy. This observation is concordant with the Medical Research Council trial of GMTZ/chemotherapy combinations that did not use thioguanine or repeated GMTZ dosing.⁴ The observed rate of severe VOD (16% ± 14%; mean ± SE) in HSCT did not differ substantially from the rate expected in high-risk unrelated donor transplants.⁷ Consistent with other reports, the two patients with severe VOD (grade IV) underwent HSCT fewer than 3 months after GMTZ exposure.^{5,13} Thus, concerns for GMTZ-associated VOD in SCT would be most relevant for patients who required a myeloablative conditioning in close temporal proximity to a GMTZ-containing reinduction regimen.

The remission reinduction rates at the MTD on arms A and B were 55% and 40%, respectively. OS and EFS rates were comparable, with differences that were not statistically significant. While these differences were not statistically significant, the modest numbers of enrolled patients limits the statistical power to detect a significant difference between treatment arms. Furthermore, treatment arm allocation on AAML00P2 was not randomized. Hence, arm A enrolled one patient with primary induction failure, while arm B enrolled eight such patients. Thus, definitive conclusions about the relative efficacy of these two treatment regimens cannot be made based on this trial.

In summary, this study determined the pediatric MTD of GMTZ in combination with two commonly used AML chemotherapy regimens. The MTD of GMTZ in combination with cytarabine and mitoxantrone was 3 mg/m² while the MTD was 2 mg/m² in combination with cytarabine and L-asparaginase. While the observed toxicities were clinically important, these toxicities do not appear substantially different from the toxicities generally seen after AML therapy. Based on other reported pediatric relapsed AML reinduction data, both treatment regimens had an acceptable remission induction rate. This trial did not test whether the addition of GMTZ provided any additional benefit above chemotherapy alone. That clinically important question is the primary aim of the ongoing COG de novo phase III AML trial, AAML0531.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Arceci RJ: Progress and controversies in the treatment of pediatric acute myelogenous leukemia. *Curr Opin Hematol* 9:353-360, 2002
2. Sievers EL, Appelbaum FR, Spielberger RT, et al: Selective ablation of acute myeloid leukemia using antibody-targeted chemotherapy: A phase I study of an anti-CD33 calicheamicin immunoconjugate. *Blood* 93:3678-3684, 1999
3. Sievers EL, Larson RA, Stadtmauer EA, et al: Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 19:3244-3254, 2001
4. Kell WJ, Burnett AK, Chopra R, et al: A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. *Blood* 102:4277-4283, 2003
5. Arceci RJ, Sande J, Lange B, et al: Safety and efficacy of gemtuzumab ozogamicin (Mylotarg(R)) in pediatric patients with advanced CD33-positive acute myeloid leukemia. *Blood* 106:1183-1188, 2005
6. Zwaan CM, Reinhardt D, Corbacioglu S, et al: Gemtuzumab ozogamicin: First clinical experiences in children with relapsed/refractory acute myeloid leukemia treated on compassionate-use basis. *Blood* 101:3868-3871, 2003
7. McDonald GB, Hinds MS, Fisher LD, et al: Venooclusive disease of the liver and multiorgan failure after bone marrow transplantation: A cohort study of 355 patients. *Ann Intern Med* 118:255-267, 1993
8. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
9. Greenwood M: The Natural Duration of Cancer: Reports on Public Health and Medical Subjects (Vol 33, No. 1). London, United Kingdom, HM Stationery Office, 1926, pp 1-26
10. Wells RJ, Adams MT, Alonzo TA, et al: Mitoxantrone and cytarabine induction, high-dose cytarabine, and etoposide intensification for pediatric patients with relapsed or refractory acute myeloid leukemia: Children's Cancer Group study 2951. *J Clin Oncol* 21:2940-2947, 2003
11. Milligan DW, Wheatley K, Littlewood T, et al: Fludarabine and cytosine are less effective than standard ADE chemotherapy in high-risk acute myeloid leukemia, and addition of G-CSF and ATRA are not beneficial: Results of the MRC AML-HR randomized trial. *Blood* 107:4614-4622, 2006
12. Lehrnbecher T, Varwig D, Kaiser J, et al: Infectious complications in pediatric acute myeloid leukemia: Analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia* 18:72-77, 2004
13. Wadleigh M, Richardson PG, Zahrieh D, et al: Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. *Blood* 8:8, 2003

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 version (via Adobe® Reader®).