Phase I Study of Oral Topotecan in Hematological Malignancies

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ABSTRACT

Purpose: In this Phase I, dose-seeking study, we investigated the dose-limiting toxicities (DLTs) and maximal tolerated dose (MTD) of oral topotecan in patients with hematological malignancies.

Experimental Design: Patients with myelodysplastic syndromes, myeloproliferative disorders, or relapsed acute myelogenous leukemia were treated with 0.6–1.9 mg/m²/day oral topotecan for 5 consecutive days on and 2 days off, for 3 weeks (15 doses/course) followed by 2–4 weeks of rest. The DLTs occurring during the first course of treatment were considered for defining the MTD. Preliminary results of antitumor activity were assessed by examining bone marrow status and peripheral blood cell counts.

Results: All 26 patients enrolled in the study were evaluable for toxicity, and 24 patients were evaluable for response. A total of 54 courses were administered. The most frequently reported nonhematological toxicities (percentage of courses) were diarrhea (57%), nausea/vomiting (50%), fatigue (24%), and mucositis (9%). DLTs included grade 3 or 4 nausea/vomiting and diarrhea at 1.9 mg/m²/day. The MTD for oral topotecan in hematological malignancies was defined at 1.4 mg/m²/day. Hematological toxicity was noted in all 26 patients and with all courses but was not considered dose-limiting. Four (17%) patients achieved a complete response, and six (25%) patients experienced hematological improvement.

Conclusions: Protracted administration of oral topotecan is safe and well tolerated in patients with hematological malignancies. At the dose-schedule used, single-agent oral topotecan has a definite activity in patients with myelodysplastic syndrome and acute myelogenous leukemia and warrants further investigation alone or in combination with other agents.

INTRODUCTION

Topotecan (Hycamtin; GlaxoSmithKline, Philadelphia, PA), a semisynthetic derivative of camptothecin, is a specific inhibitor of topoisomerase I (1). Topotecan is currently indicated for the treatment of relapsed small cell lung cancer and ovarian cancer (2–5) and has been investigated as a potential treatment for hematological malignancies (6–10). Phase I studies suggested that i.v. topotecan has antileukemic activity and could induce hematological remissions in patients with refractory AML (6) and CML in BP (6–8). Single-agent i.v. topotecan administered daily for 5 days every 4–6 weeks demonstrated significant activity to induce complete remissions in 31% of patients with RAEB, RAEB in transformation, and CMML (9). Topotecan in combination with intermediate-dose cytarabine induced CR in 61% of MDS patients and 44% of CMML patients (10). Thus, topotecan appears to be a potentially valuable addition to the limited armamentarium of antileukemic agents in the treatment of MDS, AML, and myeloproliferative disorders.

Although i.v. topotecan has shown promise in the treatment of high-risk MDS and CMML, i.v. administration may represent an inconvenience to patients, particularly when given on an extended treatment schedule. If proven effective, oral topotecan formulation may provide greater convenience and allow for more convenient outpatient treatment. In adult cancer patients, the bioavailability of oral topotecan ranges from 30% to 42%, with interpatient variabilities of 26–31% (11–14). In pediatric patients, even larger interpatient variabilities were reported, whereas intrapatient variabilities were small (15). This notion raises concerns regarding the consistency of therapeutic effectiveness of oral topotecan because the potential variability in the amount of drug absorbed may lead to greater differences in systemic drug exposure after oral than after i.v. administration of the drug.

Although disease-free status is the ultimate goal, a temporary control of disease progression, particularly in patients of advanced age, is an attractive therapeutic end point, especially if patients can be treated in the outpatient setting. Oral topotecan may also be more readily combined with other oral chemotherapeutic agents including new oral agents targeting specific signaling pathways. There are preliminary bioavailability, DLT, and MTD data for several schedules of oral topotecan in solid tumors (11–18). Due to the nature of myeloid hematological malignancies, which assign different importance to and thresholds for hematological toxicities, a Phase I study investigating...
oral topotecan in patients with myeloid malignancies such as AML, MDS, and CMML is necessary. In a single-center, Phase I, dose-seeking study, we investigated the DLT and MTD of oral topotecan in myeloid hematological malignancies.

**PATIENTS AND METHODS**

**Study Population.** Patients with primary refractory or relapsing AML after a first remission of <6 months in duration or relapsing disease after second or higher salvage therapy were eligible for the study. Previously untreated or treated patients with primary refractory or relapsed CML in accelerated phase or BP were eligible, as were previously untreated patients with Philadelphia chromosome-negative CML who were ineligible for other therapies. Also included were patients with primary refractory or relapsing high-risk MDS (RAEB or RAEB in transformation) or CMML and previously untreated patients who had high-risk MDS or CMML who were >70 years of age and/or had an Eastern Cooperative Oncology Group performance status of ≥2. To be eligible, patients were required to be >16 years of age and to have an estimated life expectancy of ≥12 weeks. Adequate hepatic (total bilirubin ≤ 2 mg/dl) and renal function (creatinine ≤ 1.5 mg/dl) were required, unless organ dysfunction was directly caused by hematological disorder.

Patients with active serious infections, clinically active peptic ulcer, chronic malabsorption syndrome, diarrhea of infectious origin, irritable bowel syndrome, or documented central nervous system disease were ineligible. Pregnant female patients were ineligible, and female patients were required to use effective contraception if they were of childbearing age. Patients had to be off investigational drugs for ≥30 days or 5 half-lives, whichever was longer. Patients were required to be off hematopoietic growth factors for at least 2 weeks. On study, the use of granulocyte colony-stimulating factor was allowed only in febrile, neutropenic patients not responding to i.v. antimicrobial and/or antifungal therapy. The study was approved by the Institutional Review Board; all patients provided written informed consent.

**Study Design and Treatment.** This single-center, Phase I study was initiated to determine a recommended dose of oral topotecan for further clinical development in patients with hematological malignancies. Pretreatment evaluation included a medical history and physical examination, complete blood count (including differential and platelet counts), Sequential Multiple Analysis-12 channel biochemical profile with liver and renal function tests, coagulation profile, and bone marrow aspirate, biopsy, cytogenetics, and cytochemical stains. Diagnosis was confirmed by morphology and histochemical stains; AML and MDS were categorized according to French-American-British criteria (19). Patients with CMML were negative for the presence of BCR/ABL as assessed by PCR.

**Treatment Schedule and Dose Escalation.** The rationale for the administration schedule was to explore prolonged exposure to the drug and use intermittent 2 days off treatment to alleviate the nausea, vomiting, and diarrhea associated with a prolonged exposure to oral topotecan (17, 20). Because the target enzyme, topoisomerase I, may be down-regulated after prolonged exposure to the drug, it was speculated that a short interruption of the exposure may also be advantageous in restoration of the topoisomerase I levels. The design was based on recent studies with oral topotecan in solid tumors. In adults, administration of topotecan twice daily for 21 days every 28 days identified gastrointestinal toxicity as DLT and determined a MTD of 0.5 mg/m² twice daily (17). In pediatric patients with solid tumors, two schedules of oral topotecan were investigated: in the first, topotecan was given once daily for 21 days/cycle, and the second explored a once daily, 5 days on/2 days off for 15 doses/cycle schedule. Both trials found 0.8 mg/m²/day to be the MTD and myelosuppression, particularly neutropenia, and, to a lesser degree, diarrhea to be the DLTs (20).

The starting dose of oral topotecan was 0.6 mg/m²/day for 5 days on and 2 days off, for 3 consecutive weeks (15 doses or 9 mg/m²/course over 17 days). Completion of each course was followed by 2 weeks of rest. If, at the end of the 2-week rest period, neutropenia and/or thrombocytopenia were caused by drug-induced myelosuppression, subsequent courses were delayed until the WBC count was >2 × 10⁹ cells/liter and the platelet count was 80 × 10⁹/liter, or until evidence of disease progression. If low counts were attributed to persistent/progressive disease (as evidenced by increased percentage of bone marrow blasts with no change or increase in the marrow cellularity and/or increase in the peripheral blast count), subsequent courses were initiated regardless of WBC and platelet counts. For patients whose grade 3/4 nonhematological toxicities failed to return to <grade 3, additional courses of therapy were delayed in 1-week increments for a maximum of 2 weeks to allow recovery to occur. If toxicities failed to resolve to <grade 3, treatment was discontinued.

The drug dose was escalated by approximately 25% increments according to predetermined schedule to 0.8, 1.1, 1.4, 1.9, and 2.4 mg/m²/day. Although both interpatient dose escalation and intrapatient dose escalation were allowed, only the results from interpatient dose escalation were used for the determination of the DLT and MTD. Each dose was adapted to the strength of available oral topotecan preparations; the final dose per square meter was rounded up to the nearest combination of 0.25- and 1.0-mg caplets. The first course of chemotherapy was administered in an outpatient or inpatient setting, and patients were followed by laboratory studies at least twice weekly.

Patients received a second course of chemotherapy at the same dose level as the first course if they experienced ≤ grade 2 nonhematological toxicity and had a favorable response to therapy. If the patient experienced ≥ grade 3 nonhematological toxicity with a favorable response to therapy, another course of treatment was administered at the next lower dose level. If the patient had an unfavorable response to therapy (stability or increase in peripheral blood or bone marrow blasts) and experienced ≤ grade 2 nonhematological toxicity (excluding nausea, vomiting, and alopecia), another course of treatment was administered at the next higher dose level, provided the patient had recovered from all toxicities, and ≥1 week had elapsed since the prior course. However, these courses were not included in the

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4 Unpublished results.
DLT analysis. Responding patients were eligible to receive additional courses at the highest dose level previously tolerated in 4–6-week intervals (depending on toxicity and blood count recovery) or until disease progression or lack of benefit. Patients who achieved CR were eligible to receive additional consolidation courses (3 weeks on/2–4 weeks off) for up to a maximum of 6 months.

Safety Definitions and Measurements. Estimation of DLT pertained only to events occurring during the first course (15 doses) of treatment. Unexpected, severe, and life-threatening nonhematological toxicity not attributed to a cause other than the study drug was considered a DLT. Nonhematological toxicity of ≥grade 3 (National Cancer Institute Common Toxicity Criteria) in severity (with the exception of fever, anorexia, alopecia, and nausea and vomiting that could be controlled with antiemetics) was considered a DLT. At least 3 patients were entered at each dose level. If none of the three patients experienced grade 3 or 4 toxicity, the dose was escalated to the next level. If 2 of 3 patients experienced grade 3 or 4 toxicity, the dose was considered above the MTD. If 1 of the 3 patients developed grade 3 or 4 toxicity at a given dose level, 3 more patients would be entered at that dose level. If none of these additional patients experienced DLT (a total of <2 of 6 or fewer patients), the dose was escalated to next level. Presence of grade ≥2 nonhematological toxicities in 2 of 3 or >2 of 6 patients defined the DLT, and the MTD was one level below. Once the MTD was determined, an additional 10 patients were treated at that dose.

Grade 3 or 4 hematological toxicity during remission or prolonged myelosuppression, defined as a hypocellular bone marrow with <5% cellularity at 6 weeks from start of treatment, required a one-dose level reduction for subsequent courses.

Supportive Care. Patients with neutrophil counts at <1.5 × 10^9 cells/liter received prophylactic treatment with oral antibacterial [trimethoprim (160 mg) and sulfamethoxazole (800 mg twice)] daily, ciprofloxacin (500 mg) twice daily, or levofloxacin (500 mg/day), antifungal [fluconazole (100–200 mg/day)], and antiviral [valacyclovir hydrochloride (500 mg/day)] agents. Prophylactic antinausea medication was administered daily for the first 5 days of the course and then administered as needed. At the first clinical signs of diarrhea, patients were given loperamide hydrochloride or diphenoxylate atropin (Lomotil). Patients with severe thrombocytopenia (platelet count < 20 × 10^9/liter) received prophylactic platelet transfusions at the discretion of the physician, in general for clinical signs of bleeding or for platelet counts below 10 × 10^9/liter. RBC transfusions were administered according to clinical symptoms, hemoglobin levels, and the tolerance of individual patients to anemia.

Efficacy Measurements. To allow comparison, we elected to use response criteria identical to those defined in our previous study of i.v. topotecan (9). A CR was defined as <5% blast cells in the bone marrow, no circulating blast cells, peripheral neutrophil count of >1 × 10^9/liter, and platelet count of ≥100 × 10^9/liter. The presence of dysplasia was not considered evidence of persistent disease because it is, in our experience, often seen after chemotherapy and also persists in patients with CR characterized by conversion of abnormal to diploid karyotype. In following the established practice at our institution, a defined duration of response was not required for definition of CR. A partial response was defined as a CR with continuous presence of ≥5% blast cells in the bone marrow, despite the number of blast cells having decreased by ≥50%. HI was achieved when ≥2 of the following occurred: platelet counts increased by 100% and >50 × 10^9/liter if the baseline platelet count was below this level; granulocyte count increased by 100% and >1 × 10^9 cells/liter if the baseline granulocyte count was below this level; and hemoglobin increased by 2 g/dl if the baseline level was <10 g/dl or marrow blasts reduced to ≤5% if the baseline level was above this level. Progressive disease was defined as any worsening of disease.

Statistical Measurements. A minimum of one course (15 doses) of treatment was required for a patient to be considered evaluable for efficacy analysis. All patients were considered evaluable for toxicity. Descriptive summary statistics were used to summarize patient characteristics and laboratory results. All observed toxicities were summarized by the dose and the course at which they occurred; incidence rates were based on the maximum intensity grade for each adverse event and patient.

Pharmacokinetics of Oral Topotecan. The pharmacokinetic parameters were obtained in six patients during their first course of topotecan at the MTD level of 1.4 mg/m^2/day. Blood samples were obtained before ingesting and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 10, and 12 h after ingestion of the first dose of the drug. Total topotecan plasma concentrations were determined using previously described extraction and validated high-performance liquid chromatography assay (12). Absolute recovery was between 85% and 90%. Inter- and intra-day coefficients of variability for standards and quality control samples were <15%. Pharmacokinetic modeling was completed using a two-compartmental structural model [model selection criteria: R^2, Akaike’s information criteria, visual inspection of plot (goodness of fit)] using the ADAPT II V4.0 pharmacokinetic model software (Biomedical Simulation Resources, University of Southern California, Los Angeles, CA).

RESULTS

Patients. The characteristics of the 26 patients treated are summarized in Table 1. The median age was 72.5 years; 20 (77%) patients were >60 years of age. At baseline, all but 2 patients were anemic, and 20 (77%) patients had hemoglobin < 10 g/dl. Twenty-three (88%) patients had platelets < 10^5/liter, and 8 (31%) patients had ANC < 1 × 10^9/liter. Sixteen (62%) patients had received prior chemotherapy, biological therapy, or both. Of the 16 previously treated patients, oral topotecan was administered as second-line therapy (11 patients) or third or later salvage therapy (5 patients).

The 26 patients received 54 courses of oral topotecan through five dose levels. Only one patient received the drug at level 6 (2.4 mg/m^2/day) as the third course of the intrapatient escalation. All 26 patients were evaluable for toxicity; 24 patients completed ≥1 course (15 doses) of treatment and were evaluable for response.

Nonhematological Toxicity. A summary of the nonhematological toxicities by dose level is provided for the first course of oral topotecan in Table 2 and for all courses in Table 3. Nausea and vomiting and diarrhea were the most frequent
nonhematological toxicities at all dose levels and were the only grade 3 or 4 toxicities reported. In most patients at the majority of dose levels, nausea, vomiting, and diarrhea were effectively controlled using antiemetics and antidiarrheal agents, respectively. There was a trend toward an increased gastrointestinal toxicity during the last 5 days of each course. Grade 3 or 4 diarrhea was observed in 1 of 20 courses administered at 1.9 mg/m²/day; two cases of fungal infection were documented, one in a patient treated with 0.6 mg/m²/day and one in a patient treated with 1.9 mg/m²/day.

There were two deaths that occurred within 30 days of the last dose of topotecan and were thus considered as treatment associated. Both were due to infectious complications. The first patient was a 68-year-old female with a 2-year history of CML treated with multiple therapies including IFN-α, busulphan, and hydroxyurea. After treatment with 1.4 mg/m²/day of topotecan, her WBC decreased from 73 × 10⁹/liter to 2.8 × 10⁹/liter on day 18, when she was admitted with pneumonia and sputum cultures positive for Pseudomonas aeruginosa and Xanthomonas maltophilia. Despite extensive supportive care and recovery of ANC to normal levels by day 26 of topotecan treatment, the patient expired on day 31 with progressive pneumonia, sepsis, and multiorgan failure. At the time of death, her WBC was 70.8 × 10⁹/liter with 86% neutrophils and a platelet count of 16 × 10⁹/liter. The second patient was a 72-year-old male with primary refractory AML characterized by a complex karyotype. His first course of topotecan (1.4 mg/m²/day) was complicated with grade 2 diarrhea and Gram-positive septicemia, which resolved after treatment with vancomycin. Five weeks after initiation of topotecan treatment, his bone marrow had 2% blasts, and he recovered normal neutrophil count with no circulating blasts. Because of persistent thrombocytopenia, the second course was delayed until day 52. His best response was trilineage H1 associated with <5% marrow blasts. The patient was admitted on day 37 of the second course with fever, pneumonia, and progression of AML. No further treatment was given, and the patient expired with symptoms of pneumonia and progressing AML.

**DLT and MTD.** The nonhematological toxicities during the first dose of oral topotecan are summarized in Table 2. The topotecan escalation schedule was carried out through dose level 5 (1.9 mg/m²/day). All patients receiving first course of topotecan at 1.9 mg/m²/day were previously treated for their disease. Nausea and vomiting and diarrhea precluded dose escalation beyond 1.9 mg/m²/day. The first patient who entered at the 1.9-mg/m²/day dose level developed grade 3 diarrhea along with fever and documented Escherichia coli septicemia. The treatment was discontinued after the patient had received 13 of the scheduled 15 doses of the first course of topotecan. Of the two additional patients who entered at this dose level, one developed grade 3 vomiting and symptoms of dehydration that required hospitalization and i.v. fluid replacement. Before the development of the grade 3 or 4 toxicity in this patient, a fourth patient initiated treatment at dose level 5. However, because two of three patients experienced grade 3 dose-limiting nonhematological toxicity, no further patients were administered topotecan at the 1.9-mg/m² dose level. Dose level 5 (1.9 mg/m²/day) was the dose at which two of three patients experienced DLT. Therefore,
the MTD estimated by the first dose of oral topotecan administered in the current schedule was determined to be 1.4 mg/m²/day.

According to the study design, the cohort of patients treated at the MTD level was expanded by an additional 10 patients. Of the total of 13 patients who received the first course at 1.4 mg/m²/day, 4 (31%) developed grade 3 diarrhea. In all 20 courses administered at this dose level, grade 1/2 nausea or vomiting was observed in 40% of courses, and grade 1/2 diarrhea was observed in 55% of courses. (Table 3). Based on the results of this study, the recommended dose of oral topotecan administered in this dose schedule is 1.4 mg/m²/day.

Hematological Toxicity. Hematological toxicity was noted in all 26 patients and with all courses administered. Before the initiation of treatment, 23 (88%) patients were severely thrombocytopenic (platelet counts < 100 x 10⁹/liter), and 17 (65%) patients had platelet counts < 50 x 10⁹/liter. Eight patients had ANC < 1.5 x 10⁹/liter, and five patients had ANC < 0.5 x 10⁹/liter.

All patients experienced worsening of thrombocytopenia and decreases in ANC; however, the degree of worsening was difficult to evaluate in previously treated patients with active disease. It was therefore evaluated in detail in 10 patients with previously untreated MDS. The time course of platelet levels and ANC was analyzed in detail in 10 chemotherapy-naïve MDS/CMML patients treated with a first course of oral topotecan at the MTD level of 1.4 mg/m²/day. The nadir of both platelet counts and ANC was reached in the second and third week of the first course and, starting during the fourth week, was followed by recovery in responding patients or return to pretreatment values in those with stable disease. The changes in platelet counts preceded those in ANC by few days only. Clinically significant thrombocytopenia-associated hemorrhage was observed in only one patient (he was diagnosed with intracranial bleeding from which he partially recovered, and he survived >30 days after the last dose of topotecan to subsequently succumb to progressive disease). In a preliminary report of this study, this death was reported as treatment associated (20). After reassessment, it is not reported here because the patient recovered, survived for >30 days after the last dose of the drug, and subsequently died of progressive disease.

The myelosuppressive effect of oral topotecan administered at various dose levels was also evaluated by comparing the bone marrow cellularity before the first course of treatment with the bone marrow cellularity within 1 week of completion of the first course (15 doses). Bone marrow biopsies before and after topotecan treatment were available for 17 of the 26 patients treated (Table 4). Results suggest that there is a dose-dependent effect of oral topotecan on the reduction of bone marrow cellularity. At the dose level of 1.4 mg/m²/day, bone marrow cellu-
tered at the 1.4-mg/m² dose level. The mean pharmacokinetic parameters obtained after ingestion of the first dose of topotecan administered to previously untreated MDS/CMML, the pharmacokinetic data were obtained from six patients, the marrow was aplastic (<10% cellularity).

**Antitumor Activity.** The antitumor activity of oral topotecan is summarized in Table 5. Of the 24 evaluable patients, 4 (17%) achieved CR, and 6 (25%) experienced HI. All of the CRs occurred in patients treated with ≥1.1 mg/m²/day of topotecan. CRs were observed in 2 of 13 (15%) patients with MDS (CR duration, 32 and 52 weeks, respectively) and in 2 of 7 (29%) patients with nonproliferative CMML (CR duration, 12 and 32 weeks, respectively). One CR was obtained in a previously untreated patient, and three CRs were obtained in previously treated patients. In patients with MDS/CMML, the CR rate was 4 of 20 patient (20%). HI was observed in 2 of 13 (15%) patients with MDS, 2 of 7 (29%) patients with CMML, 1 of 3 (33%) patients with relapsed AML (trilineage response/CR with thrombocytopenia, CRₕ), and 1 of 2 patients with Philadelphia chromosome-negative CML.

**Pharmacokinetic Parameters.** In six patients with previously untreated MDS/CMML, the pharmacokinetic data were obtained after ingestion of the first dose of topotecan administered at the 1.4-mg/m² dose level. The mean pharmacokinetic parameters were as follows: terminal half-life (T₁/₂) was 2.26 ± 0.57 h; with a time to maximal concentration (Tₘ₉₉₉₉) of 1.7 ± 0.28 h. The total clearance (CL/F) was 154 liters/h/m², and the area under the curve was 9.6 ± 3.1 mg/ml/h.

**DISCUSSION**

The availability of an oral preparation allows for the development of new treatment regimens that can be delivered, with some advantage, in the outpatient setting. Therefore, we sought to determine a recommended dose of oral topotecan for the treatment of hematological malignancies. Past experience in Phase I studies indicated that MTD in patients with myeloid hematological malignancies is approximately 2–4 times higher than the MTD in solid tumors. This applies also to i.v. topotecan: using daily bolus schedule in adults, the MTD in patients with acute leukemia (8) was 4.5 mg/m²/day × 5 days, 3 times higher than the MTD determined for the same treatment schedule in patients with solid tumors (1.5 mg/m²/day × 5 days; Ref. 5 H. M. Kantarjian and E. Estey, unpublished observations.)

21, 22). In solid tumors, the MTDs for daily (23) and twice-daily (17) oral topotecan, given over 21 days, were 0.8 and 1.0 mg/m²/day in pediatric (23) and adult (17) patients, respectively. Therefore, for our schedule, we elected to start with 0.6 mg/m²/day (9 mg/m²/course), 43% of the solid tumor MTD in adults (17), and approximately 30% of the MTD expected in hematological malignancies. The cumulative MTD delivered in our study was 21 mg/m²/15 days, comparable with the total dose of 21 mg/m² delivered at MTD level during a 21-day cycle in adults with solid tumors (17) and 16.8 mg/21 days in pediatric patients (23). In pediatric patients treated with 5 days on/2 days off schedule for total of 15 doses, the reported MTD was 0.8 mg/m²/day, corresponding to the cumulative dose of 12 mg/m² (23).

The mean pharmacokinetic parameters obtained from six patients in this study did not differ from those reported by others in adult patients with solid tumors treated with oral topotecan (13). However, with very limited number of pharmacokinetic data points, it is difficult to draw any significant conclusions to dynamic end points.

Without the consideration of hematological toxicity, the DLT was gastrointestinal and thus similar to that observed with protracted administration of oral topotecan in adults (17). If hematological toxicity was considered, however, it is likely that neutropenia and/or thrombocytopenia might have been dose-limiting, in accordance with the findings in pediatric patients with solid tumors treated with comparable regimen (23). Our schedule was designed to deliver topotecan for 5 consecutive days on and 2 days off, for 3 consecutive weeks (15 doses/course) followed by 2–4 weeks of rest between courses. It allowed us to delay the administration of subsequent courses in the presence of prolonged myelosuppression and/or persistent grade 3/4 nonhematological toxicities. With 100% compliance with dose and schedule, the median time from the end of the treatment course to the start of the subsequent course was 34 days (range, 25–58 days).

Nonhematological toxicities at the first two dose levels were rare, and grade 3 or 4 nonhematological toxicities were not reported until the dose was escalated to 1.4-mg/m²/day, ultimately becoming the DLTs, occurring at 1.9 mg/m²/day. In the majority of patients, nonhematological toxicities were manageable with antiemetics and anti-diarrheal agents. During the 2 days “off,” nausea and diarrhea subsided in most patients, thus providing symptomatic relief, particularly after second 5-day cycle. This and possibly also the use of lomotil as an alternative to loperamide may explain a more successful control of diarrhea as compared with the experience of others with protracted use of oral topotecan (17). Grade 1 or 2 diarrhea (55%) and nausea or vomiting (40%), reported in the 20 courses administered at the MTD dose, appeared to subside during the 2 days “off.” The frequency and, to a lesser degree, the severity of diarrhea increased during the last 5 days of treatment (days 12–17 of the cycle), when lomotil was required for effective control of diarrhea in some patients in whom loperamide provided suboptimal control. A similar, time-related onset of diarrhea after day 12 of treatment was noted in patients with solid tumors treated with oral topotecan twice daily for 21 days (17). The lack of effectiveness of loperamide in these patients may also have been related to the treatment schedule, which, unlike ours, continued.

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**Table 5** Response of patients treated with at least one full course of oral topotecan by dose level and treatment history

<table>
<thead>
<tr>
<th>Dose level (mg/m²/day)</th>
<th>Patients (n)</th>
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<th>Previously untreated</th>
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<td>0</td>
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a Dose level at which the best response was observed irrespective of prior treatment.

SD, stable disease; PD, progressive disease.
without interruption and for 21 days. Noticeably, only one of the patients experienced grade 3 or 4 nonhematological toxicity during the first course at doses ≤1.4 mg/m²/day topotecan (≤21 mg/m²/course). This compares favorably with the frequency of grade 3 or 4 gastrointestinal toxicities observed in MDS and CMML patients treated with i.v. MTD of topotecan (10 mg/m²/ course in a 5-day continuous i.v. infusion; Ref. 9). Importantly, mucositis, which represents a frequent and DLT with continuous i.v. infusion of topotecan (6, 7, 9), was rarely observed with the current oral topotecan schedule.

Our results are complementary to those reported by Cancer and Leukemia Group B in a study that investigated two schedules of oral topotecan (24). In that study, 90 patients with MDS received topotecan 1.2 mg/m² twice a day for 5 days or once daily for 10 days, every 21 days. Of the 77 patients with available nonhematological toxicity data, 13% of those treated with the 5-day oral topotecan schedule and 10% of those treated with the 10-day oral topotecan schedule experienced grade 3 or 4 diarrhea compared with 3 (12%) patients in the current study.

The reported frequency of febrile episodes was 85% in MDS/CMML patients treated with continuous i.v. infusion of topotecan at MTD level (9) compared with 35% observed in the present study. In MDS patients treated with single-agent azacytidine, infectious episodes were thought to be related to treatment in 20% of previously untreated patients with MDS, included in a randomized trial of azacytidine versus supportive care (25). It can be speculated that derangement of the integrity of the epithelium of the gastrointestinal tract is a significant factor contributing to the occurrence of observed bacterial and fungal infections in severely myelosuppressed patients receiving agents with gastrointestinal toxicity. Protecting the gastrointestinal cells from cytotoxic damage may ameliorate septic events. Indeed, a recent report documented a reduced bacteremia, particularly of intestinal origin, in leukemia patients receiving high-dose chemotherapy and rhIL-11 and suggested gastrointestinal protective effect of rhIL-11 (26). Our recent study with idarubicin and high dose 1-β-D-arabinofuranosylcytosine with and without rhIL-11 suggested a protective effect of rhIL-11 as well,6 suggesting a potential future approach to decrease gastrointestinal side effects. The number of patients with febrile neutropenia was similar in the Cancer and Leukemia Group B study, which used 10 days and 5-day courses of oral topotecan, and our observation (30% and 19% versus 35% in the current study). However, the patient population in the present study included previously treated MDS and also relapsed/refractory AML patients, populations with higher risk for infections. Combined, these results suggest that an oral formulation of topotecan in MDS patients is feasible and should be more fully investigated to determine the optimal dose schedule.

Previously, continuous i.v. infusion of topotecan has been shown to induce CR in patients with MDS and CMML (9). Of 60 patients treated with 2 mg/m² topotecan by continuous i.v. infusion over 24 h for 5 days, 32% achieved CR, including 11 of 30 (37%) MDS patients and 8 of 30 (27%) CMML patients. In the current study, 4 of 20 (20%) MDS/CMML patients treated with oral topotecan achieved a CR. The lower threshold dose for clinical response was 1.1 mg/m²/day, suggesting a dose-response relationship. The results of the present study may be compared with results reported for other single chemotherapeutic agents, e.g., cytarabine, azacytidine, and decitabine (25, 27–29). For example, approximately 15% of MDS and CMML patients treated with low-dose cytarabine either alone (28, 29) or in combination with granulocyte macrophage colony-stimulating factor (27) achieved a CR, whereas a CR rate of 9% has been reported for azacytidine (25), and a CR rate of 20% has been reported for decitabine (30). Although the current study was not designed to evaluate the efficacy of oral topotecan in MDS patients, the preliminary data suggest that oral topotecan might potentially be a valuable agent in the treatment of MDS and CMML.

An intermittent dosing of topotecan may be better tolerated in the setting of a protracted exposure and possibly also more readily combined with other agents, particularly if the oral formulation of topotecan is used. Because topotecan is an S-phase-specific drug, it may be more active when administered over a prolonged period of time. Compared with i.v. administration, an oral formulation provides convenience for prolonged outpatient treatment, potentially leading to improved quality of life for patients. This may be particularly important for patients with multiple comorbidities. These considerations are further supported by the results of the current study, in which fewer patients treated at the MTD level experienced febrile episodes and severe gastrointestinal toxicity when compared with patients treated with the MTD of i.v. topotecan (8).

The results of this dose-seeking study demonstrate that at doses inducing responses in patients with MDS and CMML, oral topotecan is well tolerated and suitable for outpatient management of patients with hematological malignancies. For future Phase II studies in patients with hematological malignancies, we recommend a dose of 1.4 mg/m²/day of oral topotecan for 3 cycles consisting of 5 consecutive days on and 2 days off treatment, followed by 2–4 weeks of rest between courses.

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