Cancer Therapy: Clinical

Tumor O\textsuperscript{6}-methylguanine-DNA Methyltransferase Inactivation by Oral Lomeguatrib

Amanda J. Watson\textsuperscript{1}, Ami Sabharwal\textsuperscript{2}, Mary Thomcroft\textsuperscript{1}, Gail McGown\textsuperscript{1}, Richard Kerr\textsuperscript{3}, Stana Bojanic\textsuperscript{2}, Zahir Soonawalla\textsuperscript{4}, Alexandra King\textsuperscript{5}, Andrea Miller\textsuperscript{5}, Sue Waller\textsuperscript{2}, Hing Leung\textsuperscript{6}, Geoffrey P. Margison\textsuperscript{1}, and Mark R. Middleton\textsuperscript{2}

Abstract

Purpose: A major mechanism of resistance to chloroethylnitrosoureas and methylating agents involves the DNA repair protein O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT). We sought to determine the dose of oral 6-(4-bromo-2-thienyl) methoxy purin-2-amine (lomeguatrib), a pseudosubstrate inactivator of MGMT, required to render active protein undetectable 12 hours after dosing in prostate, primary central nervous system (CNS), and colorectal cancer patients.

Experimental Design: Lomeguatrib was administered orally as a single dose (20-160 mg) \sim 12 hours before tumor resection. Dose escalation was projected to continue until grade 2 toxicity or until complete inactivation of tumor MGMT was encountered. Total MGMT protein levels were quantified by ELISA, and active protein levels were quantified by biochemical assay. MGMT promoter methylation was determined in glioblastoma DNA by methylation-specific PCR.

Results: Thirty-seven patients were dosed with lomeguatrib, and 32 informative tumor samples were obtained. Mean total MGMT level varied between tumor types: 554 ± 404 fmol/mg protein (±SD) for prostate cancer, 87.4 ± 40.3 fmol/mg protein for CNS tumors, and 244 ± 181 fmol/mg protein for colorectal cancer. MGMT promoter hypermethylation did not correlate with total protein expression. Consistent total MGMT inactivation required 120 mg of lomeguatrib in prostate and colorectal cancers. Complete consistent inactivation in CNS tumors was observed only at the highest dose of lomeguatrib (160 mg).

Conclusions: Total MGMT inactivation can be achieved in prostate, primary CNS, and colorectal cancers with a single administration of 120 or 160 mg lomeguatrib. The dose needed did not correlate with mean total MGMT protein concentrations. One hundred twenty to 160 mg/d of lomeguatrib should be administered to achieve total MGMT inactivation in future studies. Clin Cancer Res; 16(2); 743–9. ©2010 AACR.

Chloroethylnitrosoureas such as 1,3-bis-(2-chloroethyl)-1-nitrosourea and methylating agents such as temozolomide are cytotoxic by virtue of adducts formed at the O\textsuperscript{6} position of guanine (1–3). Resistance to these O\textsuperscript{6}-alkylating agents can be conferred by the repair protein O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT), which removes the alkyl group from the O\textsuperscript{6} position on guanine in a stoichiometric, autoinactivating reaction (3, 4). It covalently transfers the alkyl group to its active site cysteine either before chloroethylnitrosouanine initiated DNA interstrand cross-links can form or before O\textsuperscript{6}-methylguanine:thymine mispairing results from further rounds of replication. MGMT is unique in its ability to remove DNA adducts independently rather than through multienzyme complexes, as is the case in most other DNA repair systems.

6-(4-Bromo-2-thienyl) methoxy purin-2-amine (lomeguatrib) is an orally bioavailable potent pseudosubstrate for MGMT. The drug was developed with the aim of inactivating MGMT, rendering cells more sensitive to the cytotoxic effects of O\textsuperscript{6}-alkylating agents. Covalent transfer of the bromoethyl group on lomeguatrib to the active site cysteine inactivates MGMT. Lomeguatrib has shown promising activity in sensitizing a variety of human tumor xenografts to the growth-inhibitory effects of O\textsuperscript{6}-alkylating agents, including temozolomide and 1,3-bis-(2-chloroethyl)-1-nitrosourea, at the expense of only limited additional toxicity (5, 6).
Translational Relevance

The DNA repair protein O\(^6\)-methylguanine-DNA methyltransferase is a major factor in resistance to chloroethylnitrosureas. Lomeguatrib is a small-molecule inactivator of O\(^6\)-methylguanine-DNA methyltransferase, with the potential to enhance the cytotoxicity of chemotherapy. This report describes a phase 0 trial to establish the biologically effective dose of lomeguatrib to use in future studies of the agent.

Following a phase I study of combination treatment with lomeguatrib and temozolomide (7), a randomized phase II study using this combination in over 100 patients with metastatic melanoma has been reported (8). Patients were treated with 40 to 80 mg lomeguatrib with 125 mg/m\(^2\) temozolomide alone orally on days 1 to 5 every 28 days for up to six cycles. The lomeguatrib dose was selected based on tumor depletion at 4 hours in six melanoma patients included in the phase I trial. The efficacy of combination treatment with lomeguatrib and temozolomide was found to be similar to that of temozolomide alone in terms of response rates and median time to disease progression (13.5% versus 17.3% and 65.5 versus 68 days, respectively). This may have been due to the scheduling of lomeguatrib, which permitted rapid recovery of tumor MGMT. Tumor biopsies from patients showed early recovery of MGMT activity, within 24 hours, even when 60 or 80 mg of lomeguatrib was given daily (8).

Data are needed on the effects of lomeguatrib in other tumor types to determine the doses best used in tumor site-specific combination studies. Our study focused on four tumor types—primary breast, prostate, and central nervous system (CNS) cancers and primary or secondary colorectal cancers. These were selected on the basis of results from work on human xenograft models, which showed that lomeguatrib enhanced the antitumor effects of temozolomide in these tumor types (9, 10). Tumor types were also chosen to provide a range of MGMT activities, according to the literature (11).

The primary aim of this study was to determine the dose of oral lomeguatrib required to render active MGMT undetectable 12 hours after dosing in primary breast, prostate, and CNS tumors and primary or secondary colorectal tumors as measured by biochemical assay. The 12-hour time point was chosen based on pharmacokinetic and pharmacodynamic results from our phase I trial of lomeguatrib with temozolomide (7). Given that some of the tumors might not have expressed the MGMT protein and would have shown no activity even before the lomeguatrib dosing, it was also necessary to quantify total MGMT protein expression (both active and inactive), and for this, we used an antibody-based method. In this way, we could estimate the extent to which MGMT had been inactivated by lomeguatrib treatment. We also evaluated the safety of lomeguatrib as a single agent. In CNS tumors, MGMT promoter methylation status was determined in DNA extracted from tumor aliquots to assess its relationship with MGMT protein expression levels, and to determine the intratumoral heterogeneity in the methylation status.

Patients and Methods

Eligibility. Patients due to undergo elective surgery for removal of a primary breast, prostate, or CNS tumor, or primary or secondary colorectal cancer were identified from the two clinical centers. To be eligible for the study, patients needed to be ages 18 y or over with elective surgery for tumor removal scheduled within 14 d. Histologic or cytologic confirmation of cancer was required for breast and colorectal patients. In the absence of histologic or cytologic confirmation of cancer for CNS and prostate patients, strong radiological suspicion or a prostate-specific antigen diagnosis (≥20 μg/L) were necessary, respectively. Patients whose subsequent histology did not confirm a primary CNS (defined as glioblastoma multiforme or anaplastic astrocytoma) or prostate cancer were excluded from analysis of tumor MGMT inactivation.

This study was conducted under the auspices of Cancer Research UK in accordance with the principles of the International Conference on Harmonisation of Good Clinical Practice guidelines and the Declaration of Helsinki. The trial was approved by the Cancer Research UK Independent Ethics Committee and by the Local Research Ethics Committee of each trial center. All patients enrolled in the study gave written informed consent.

Treatment and dose escalation. Lomeguatrib (KuDOS Pharmaceuticals Ltd) was administered orally ~12 h before tumor resection. Patients were requested to fast for 2 h predosing and postdosing and were advised to swallow the lomeguatrib capsules whole so as not to interfere with the enteric coating. Five dose levels of lomeguatrib were to be studied in each tumor type: 20, 40, 80, 120, and 160 mg. These were selected to include the dose range found from phase I work to completely deplete MGMT in a variety of solid tumors, i.e., 40 to 80 mg/d (7). Dose levels above and below this range were included to take into account the different levels of MGMT expression in the tumors studied in anticipation of the possibility that different doses of lomeguatrib might be required to engender complete MGMT depletion (10, 11). The dose range also reflected data from studies with the MGMT pseudosubstrate O\(^6\)-benzylguanine, showing that approximately thrice the dose of inactivator is required to deplete MGMT in tumor as in peripheral blood mononuclear cells (PBMC; ref. 12).

Initially, patients were enrolled in cohorts of three to allow an assessment of the safety of each lomeguatrib dose. If any of the three patients had detectable active tumor, MGMT escalation continued. In the event of all three patients exhibiting no active protein, a further three patients...
were to be recruited at that dose level to confirm the observation. Dose escalation was to cease in the event of an adverse event greater than grade 1, except for grade 2 nausea and vomiting, which was probably, possibly, or almost certainly related to lomeguatrib. As safety data emerged from other studies, dose escalation was permitted immediately after any patient showed active residual tumor MGMT. Due to poor recruitment, the breast cancer arm of the study was discontinued.

**Toxicity and response evaluation.** Pretreatment evaluations were performed in the 2 wk before the anticipated date of surgery. These involved a complete medical history and physical examination including performance status and vital signs. The results of preoperative baseline blood tests performed within the same time interval documenting bone marrow, renal, and hepatic function, and glucose, uric acid, and bone chemistry were recorded from patient notes. Patients were assessed for safety and toxicity from the time of informed consent until end of treatment evaluation 28 d after lomeguatrib administration. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Patients were formally assessed preoperatively as outlined above, again on the day after surgery and 28 d after dosing. Postoperative assessments involved a physical examination including vital signs. Full blood count and biochemistry profile were done and adverse events and concurrent medication were recorded. If any adverse events attributable to lomeguatrib occurred, the patient was followed up monthly until the resolution of the events. The safety profile at each dose level was reviewed before the next group of patients was recruited. In the event that surgery was delayed such that the tumor could not be removed within 6 to 18 h of the lomeguatrib dose, that patient was replaced. All tumor samples were analyzed to confirm that tumor tissue was removed at operation, and that the histology conformed to that under investigation in the protocol. Patients with no tumor found or whose histology was inappropriate were replaced.

**Pharmacodynamics.** At the time of surgery, ~12 h after lomeguatrib dosing, between one and six representative samples from the tumor were collected and immediately frozen on dry ice before storage at ~70°C before determination of MGMT activity and total protein (13, 14). Samples obtained <6 h after dosing or >18 h afterwards were excluded from analysis. Ten milliliters of blood were collected in a universal tube containing 100 μL 0.5 mol/L EDTA for PBMC isolation and the analysis of MGMT activity (13). The pharmacodynamic effect of lomeguatrib was assessed by measuring the active and total MGMT protein in each tumor type to determine the degree of MGMT inactivation. In tumors where more than one sample was provided for analysis, the mean value was calculated. The MGMT activity assay was biochemical, measuring the transfer from a DNA substrate of radiolabeled methyl groups to MGMT protein in the sample under standard conditions (13). Total MGMT protein (active and inactive) was also determined by a validated ELISA to confirm protein expression in the tumor before lomeguatrib administration, and to allow the calculation of the degree of MGMT inactivation (13). Only samples showing evidence of MGMT protein expression (i.e., greater than the lower limit of quantitation, i.e., >30 fmol/mg protein) by this method were eligible for analysis. MGMT activity was reported as completely inactivated if the level of active MGMT was <32.5 fmol/mL of tissue sonicate. MGMT activity was also measured in posttreatment PBMC samples as a confirmation of lomeguatrib ingestion.

**MGMT promoter methylation status.** Given the emerging role of tumor MGMT promoter methylation in selecting glioblastoma patients for chemotherapy (14), we extracted DNA from CNS tumor sonicates using a Qiagen Blood and Cell Culture DNA mini kit (Qiagen Limited). Our method was similar to that of Hegi et al. (14), but did not require a two-stage PCR as we had large amounts of DNA available. Briefly, bisulfite conversion of DNA (500 ng) was done using EZ DNA Methylation-Gold kit from Zymo Research (Cambridge Bioscience). PCR amplification was undertaken using 0.8-μmol/L concentrations of the following primers (synthesized by MWG, Eurofins Genetic Services Ltd): methylation-specific primers forward, 5′-TTCGACGTTTCGTAGGTTTTTGT; reverse, 5′-GCACCTTCCGAAAAAGCAAGCA; and unmethylated DNA primers forward, 5′-TTTGTGGTTTGTGATTTGTTTGTGTTT; reverse, 5′-AACCACACTCTTTCCAAAAAAllelAACA, with 200 μmol/L deoxynucleoside triphosphates. PCR conditions were as follows: 97°C for 5 min, 80°C hold, add 0.2 μL Promega Go Taq DNA Polymerase (Promega Ltd, Chilworth Research Centre), then 35 cycles of 95°C for 30 s, 59°C for 30 s, and 72°C for 30 s, followed by 72°C for 10 mins and 4°C hold. Controls for the PCRs were InterGen CpGenome Universally methylated DNA as positive control and Promega Human Male DNA and double-distilled water as negative controls. Methylation patterns were scored as indicated. PCR products were run on a 2% agarose gel stained with ethidium bromide and were visualized with UV. A 100-bp marker ladder was loaded to enable size estimation. If methylation-specific primers gave a product of the correct size, then the sample DNA was considered to be methylated, and if unmethylated primer gave a product, it was considered unmethylated.

**Results**

**Patients and dose escalation.** Of the 40 patients enrolled in the study, 37 received lomeguatrib. A patient with colorectal cancer liver metastases had their hepatectomy cancelled due to the diagnosis of new lung metastases, and a prostate cancer patient declined participation after registration. The third patient was not dosed preoperatively in error.

All 37 patients given lomeguatrib were evaluable for toxicity, but only 32 patients provided tumor specimens informative in assessing MGMT inactivation. Two patients had tumor samples taken that had no detectable MGMT,
active or inactive. Tumor material taken from a third patient was insufficient for analysis and tumor was not provided from a fourth. A fifth patient with radiological evidence of a CNS tumor was found to have primary CNS lymphoma, and was excluded from the analysis.

The number of patients with each tumor type who were given lomeguatrib at each dose level is given in Table 1. All of the patients had a tumor excised within the permitted 6- to 18-hour window after lomeguatrib dosing, with the interval ranging from 8 to 17 hours and 40 minutes. The median time to tumor sampling was 12 hours in CNS tumors, but slightly longer for the other two tumor types (Table 1). There was no correlation between the extent of MGMT inactivation and the time to tumor sampling (data not shown).

**MGMT depletion.** With one exception, patients given lomeguatrib exhibited very low or no active MGMT in PBMCs. One patient with a CNS tumor given 20 mg of drug had 16.7 fmol/μg DNA active MGMT, a finding more consistent with pretreatment levels found in our other studies. The percentage of inactive tumor MGMT in this individual, at 25%, was lower than that observed in the other two CNS patients at this dose level.

Total tumor MGMT varied considerably between tumor types (Fig. 1), with prostate cancers having the highest levels (mean, 554 ± SD 404 fmol/mg protein) and CNS tumors the lowest (mean, 89.9 ± 44.5 fmol/mg protein). Colorectal tumors showed intermediate levels of total protein (244 ± 181 fmol/mg protein).

Across all three tumor types, increasing doses of lomeguatrib were associated with an increasing proportion of inactive MGMT in tumors (Table 1). There were marked differences in the proportion of MGMT that was inactive between the tumor types. These differences were most striking at the lowest dose level where 25% to 70% of MGMT was inactive in CNS tumors; 77% to 89% was inactive in colorectal cancer; and 94% was inactive in prostate cancer. MGMT protein levels in subdivided CNS tumor samples showed variable heterogeneity in total MGMT levels (Fig. 2).

**MGMT promoter methylation.** The MGMT promoter region in DNA isolated from all six of the CNS tumor extracts contained unmethylated DNA. Three of the tumors also contained methylated DNA. Multiple aliquots from individual tumors gave consistent results in all six cases (Fig. 2).

**Toxicity.** Lomeguatrib was very well tolerated with only three grade 1 adverse events recorded that may have been related to the drug. These did not seem to be dose related and all resolved spontaneously. They included an abnormal sensation in the abdomen and two instances of raised liver enzymes (raised transaminases, γ-glutyltransferase, and alkaline phosphatase) between 1 and 4 weeks after the administration of the study drug.

Several adverse events that were recorded were considered to be secondary to the patient's surgery and not due to lomeguatrib administration. Of these, five episodes were serious by virtue of the need for, or prolongation of, hospitalization of the patient. One patient experienced pain and blurred vision in their right eye (both grade 2), assessed as secondary to their right temporal craniotomy. There were two instances of grade 3 increases in alanine

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**Table 1. Effect of lomeguatrib on tumor MGMT**

<table>
<thead>
<tr>
<th></th>
<th>Primary CNS tumor</th>
<th>Colorectal cancer</th>
<th>Prostate cancer</th>
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<tr>
<td>Number</td>
<td>9</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Median time (h)</td>
<td>12 (8.0-14.5)</td>
<td>14.5 (11.75-17.67)</td>
<td>13.83 (12.67-16.25)</td>
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<td></td>
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<td>removal (range)</td>
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<td></td>
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<tr>
<td>Mean total</td>
<td>89.9 ± 44.5</td>
<td>244 ± 181</td>
<td>554 ± 404</td>
</tr>
<tr>
<td>MGMT (fmol/mg</td>
<td>± SD</td>
<td>± SD</td>
<td>± SD</td>
</tr>
<tr>
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<td>Range of total</td>
<td>38-165</td>
<td>47-547</td>
<td>47-1,136</td>
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<td>MGMT (fmol/mg</td>
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<td>protein)</td>
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| Lomeguatrib      | Patients with   | Mean % MGMT | Patients with   | Mean % MGMT | Patients with   | Mean % MGMT |
|                  | total MGMT      | inactivation| total MGMT      | inactivation| total MGMT      | inactivation|
| dose (mg)        | inactivation    | (range)     | inactivation    | (range)     | inactivation    | (range)     |
| 20               | 0/3             | 43 (25-70)  | 0/3             | 82 (77-89)  | 0/1             | 94          |
| 40               | 0/1             | 46          | 1/2             | 61 (22-100) | 1/1             | 100         |
| 80               | 0/1             | 57          | 2/3             | 98 (93-100) | 2/3             | 98 (95-100) |
| 120              | 0/2             | 73 (62-85)  | 5/6             | 100         | 2/3             | 100 (99-100)|
| 160              | 2/2             | 100         |                  |             |                 |             |

NOTE: Two patients with breast cancer were given 20 mg lomeguatrib; one provided an informative tumor biopsy specimen in which all the MGMT was inactivated.
transaminase in patients following hepatic resections. One patient developed a grade 3 chest infection and a grade 4 pulmonary embolus, and a further patient suffered a grade 3 ileus.

Discussion

The aim of this trial was to determine the dose of lomeguatrib that reliably inactivated tumor MGMT in patients with one of four cancers. The use of a pharmacodynamic end point to determine the dose of lomeguatrib for use in future studies was based on the expectation that MGMT inactivation was likely to be achievable at doses well below the maximum tolerated dose of the drug. The range of lomeguatrib doses was selected based on the findings of our phase I trial where 40 to 80 mg of lomeguatrib given orally produced total MGMT inactivation in both tumor and PBMCs 4 hours after dosing (9), and by the constraints inherent in the 10 mg capsule size available to us.

Complete MGMT inactivation was seen in primary CNS tumor biopsies after treatment with 160 mg lomeguatrib, and was first observed in colorectal and prostate cancer with 40 mg lomeguatrib. However, consistent inactivation was only observed in these two tumor types with 120 mg lomeguatrib. Very slow recruitment led to the abandonment of the breast cancer arm of the study, although the only patient given lomeguatrib (20 mg) showed complete inactivation of MGMT. The originally specified end point of the study, to define a dose of lomeguatrib that achieved total MGMT inactivation in six of six samples for each tumor type, was not achieved mainly due to slow accrual and the imminent expiry of the lomeguatrib stock. Nevertheless, depletion was complete in two CNS and prostate and five colorectal patient tumors.

PBMC samples were used to check that ingestion and absorption of lomeguatrib had taken place. In all but one case, absent or very low levels of active MGMT was absorbed. It may be that concurrent antiepileptic medication (300 mg of phenytoin daily) affected drug metabolism or that recovery of active MGMT was already in progress at the time of sampling, which was 12 hours and 25 minutes after lomeguatrib administration.

Substantial variation in MGMT protein levels were seen both between and within tumor types, as previously reported (11). The mean total MGMT levels in the three main tumor types assessed, with an increase from primary CNS tumors to colorectal cancer to prostate cancer, were in keeping with previous reports on xenograft models and clinical tumor sample series (10, 11).

This is the first study to report levels of active and inactive MGMT in tumor biopsies. We did not anticipate the variation in the proportion of inactive to total MGMT between the three tumor types studied. It may be that the basis for this observation is that tumor penetration of lomeguatrib differs between prostate, colorectal, and CNS cancers. Alternatively, the proportion of active to inactive MGMT may inherently differ between the tumor types. The study design did not mandate the collection of tumor without lomeguatrib administration, which may have resolved this issue. If the effects of the inactivator are tissue specific, this has implications for the indications in which the drug should be evaluated. To date, results using daily doses of 40 to 80 mg in melanoma and colorectal cancer have been disappointing, but our findings suggest that prostate cancer may be a better target for treatment.

If the proportion of active to inactive repair protein differs between tumors, this has implications for the methods used to evaluate MGMT in clinical specimens. In particular, immunohistochemical techniques that fail to distinguish active from inactive protein will not provide an accurate assessment of relative repair capacity when compared across tumor types.

The proportion of MGMT that was inactive broadly increased with increasing doses of lomeguatrib in all three tumor types. We observed no correlation between the dose of lomeguatrib required for inactivation and mean total MGMT in the three cancers. Previous reports, based...
on studies in cell culture, indicated that following its action on methylated DNA, MGMT is ubiquitinated and degraded by proteasome activity. We cannot exclude the possibility that such an event may have contributed to some elimination of lomeguatrib-inactivated MGMT. However, inactive MGMT was clearly abundant, so it may be that this is not a rapid effect in tumors, or perhaps that lomeguatrib-inactivated protein is not as effective a substrate for ubiquitination and proteasome degradation.

In keeping with previous findings, oral lomeguatrib was well tolerated at the dose levels studied (8, 9, 15, 16). It is extremely unlikely to have single agent antitumor activity and it will only be used in combination with cytotoxic agents. To this end, the results seen in primary brain tumors, the mainstay of treatment for which is temozolomide, are of particular interest. MGMT promoter methylation status is currently used in Europe to stratify patients to be treated with temozolomide alongside radiotherapy (14). In CNS tumors samples, we observed the presence of unmethylated MGMT promoter in all of the samples and the presence methylated promoter in half of the samples. There was no correlation between promoter methylation and protein expression; indeed, the highest level of MGMT expression was seen in one of the samples that contained methylated DNA. This raises some doubts about the validity of CNS tumor MGMT promoter methylation as a predictor of MGMT expression levels, but might indicate that the observed correlation between MGMT promoter methylation and response to therapy is not attributable to MGMT expression.

Studies have been conducted with lomeguatrib and temozolomide in a variety of solid tumors in the phase I setting. The main toxicities seen with the combination treatment were hematological, and required the standard single agent dose of temozolomide to be reduced by 40 to 60% depending on the duration of lomeguatrib administration. A regimen of oral 40 mg/d lomeguatrib with 125 mg/m² temozolomide for days 1 to 5 was suggested for further evaluation (9). The temozolomide dose that could safely be administered with the higher levels of lomeguatrib required and could reliably achieve complete MGMT inactivation in primary brain tumors will need to be established. Ranson et al. (8) established that MGMT recovers rapidly after treatment with lomeguatrib and temozolomide in patients with metastatic melanoma. However, it may be that although 120 or 160 mg doses of lomeguatrib are required to inactivate tumor MGMT, lower doses are needed to maintain inactivation. We have no data to show how long inactivation lasts, and the short half-life of lomeguatrib (1.5-2 hours) suggests that maintaining activation may require twice daily dosing.

The results of our study shed new light on previous trials with lomeguatrib in combination with temozolomide in metastatic colorectal cancer. A phase II trial to evaluate lomeguatrib in combination with temozolomide in metastatic colorectal cancer has recently been reported (16). Patients received 40 mg lomeguatrib with temozolomide (50-200 mg/m²) daily by mouth for 5 days every 4 weeks. Despite the consistent depletion of MGMT in PBMCs, no clinical responses to treatment were seen. This negative result can be explained by colorectal cancer being inherently insensitive to temozolomide, and MGMT not being a significant factor in this resistance. Deficient mismatch repair, for example, can lead to tolerance of methylation damage. Our results suggest that inadequate inactivation of MGMT in tumor, which was not measured in the trial, is an additional possible reason for the lack of effect observed.

In summary, total MGMT depletion can be achieved in primary CNS, colorectal, and prostate cancers with a single administration of lomeguatrib. The doses required were 120 mg for colorectal and prostate cancers and 160 mg for CNS tumors. Lomeguatrib is well tolerated at these doses, which are recommended for future studies in these tumor types.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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Amanda J. Watson, Ami Sabharwal, Mary Thorncroft, et al.


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