

Farnesyltransferase Inhibition in Hematologic Malignancies: The Clinical Experience With Tipifarnib

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Abstract Increased understanding of the cellular mechanisms associated with various malignancies has allowed researchers to develop agents that selectively target the cellular proteins and pathways implicated in the pathogenesis of malignancy. Tipifarnib is a specific and potent farnesyltransferase inhibitor that demonstrates *in vivo* and *in vitro* activity against a variety of human cancers. Although tipifarnib was initially thought to target the Ras protein, recent evidence suggests that the presence of *ras* mutations is not necessary for the antitumor effects of tipifarnib, and that tipifarnib may exert its effects downstream of Ras. The oral administration and favorable toxicity profile of tipifarnib, combined with its activity in a variety of intracellular pathways that have been implicated in the pathogenesis of hematologic malignancies, make it an especially attractive agent for use in patients with acute myeloid leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia (CML), and multiple myeloma. Because hematologic malignancies are likely driven by multiple genetic aberrations, the most effective treatment strategy will likely combine multiple agents with complementary mechanisms of action. Thus, additional studies of combination regimens that incorporate tipifarnib with other antineoplastic agents are crucial. Early results from studies combining tipifarnib with imatinib or etoposide in CML and AML have been promising and warrant further evaluation in larger clinical trials.

Increased understanding of the cellular mechanisms associated with various malignancies has allowed researchers to develop agents that selectively target the cellular proteins and pathways that have been implicated in the pathogenesis of malignancy. Such compounds may prove effective in overcoming or preventing the mechanisms of failure observed with standard therapies in some hematopoietic malignancies. Indeed, the development of drugs directed against specific targets has led to high rates of remission; however, the emergence of resistance has also been seen in a subset of patients. Thus, new compounds directed toward alternative proteins and pathways involved in tumorigenesis may

Keywords

acute myeloid leukemia; chronic myelogenous leukemia; farnesyltransferase inhibitor; hematologic malignancy; tipifarnib

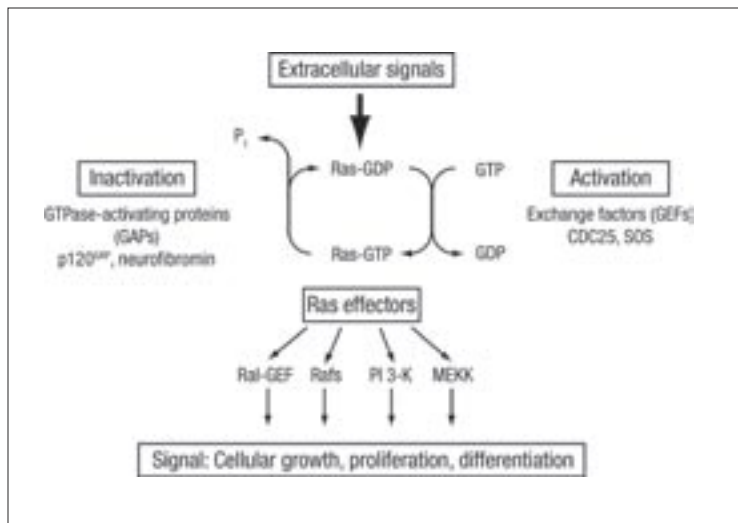


Figure 1. The activation of Ras affects several cellular signaling pathways that control cellular growth, proliferation, and differentiation.

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overcome resistance and increase response rates. This article provides an overview of the development of the farnesyltransferase inhibitor (FTI) tipifarnib (Zarnestra, Johnson & Johnson) and reviews the clinical experience to date with tipifarnib (alone or in combination) in hematologic malignancies.

Development of FTIs

When they were first discovered, FTIs were thought to target the Ras family of proteins (including K-Ras, N-Ras, and H-Ras), which are involved in the key cellular functions of proliferation, survival, and differentiation (Figure 1).¹⁻⁶ Ras must be transferred from the cytoplasm to anchor on to the inner cell membrane by prenylation (or farnesylation), which is mediated by farnesyltransferase, an enzyme that catalyzes the transfer of a farnesyl moiety to the sulfhydryl cysteine of the CAAX motif of substrate proteins.^{2,5} Notably, mutations and abnormal *ras* gene expression (especially those involving *N-ras*) have been detected in 10–15% of patients with myelodysplastic syndromes (MDS) and 15–25% of patients with acute myeloid leukemia (AML).⁷ In addition, *ras* mutations and abnormalities may cause constitutive activation of the Ras protein.

The important role of Ras in cellular signal transduction—combined with the high frequency of Ras activation in cancer—has made it an attractive target for the development of new anticancer agents such as FTIs. It should also be noted that although H-, N-, and K-Ras proteins are naturally farnesylated, K-Ras and possibly N-Ras become geranylgeranylated when human cancer cells are treated with FTIs, and the presence of this alternative pathway has raised questions about the

mechanism by which FTIs suppress cancer cell growth.⁸ Regardless of the precise mechanism of their antitumor activity, FTIs are now known to affect a wide range of intracellular signaling proteins and pathways, including RhoB, centromere-associated proteins, Pi3K/AKT-mediated growth factor, and adhesion-dependent survival pathways (Figure 2).⁹⁻¹³

Tipifarnib is a specific and potent orally available FTI that has demonstrated *in vivo* and *in vitro* activity against a variety of human cancers.^{14,15} Although initially thought to target Ras, recent evidence suggests that the presence of *ras* mutations is not necessary for the antitumor effects of tipifarnib; instead, other farnesylated proteins are thought to be involved.^{7,9,16,17} The oral administration and favorable toxicity profile of tipifarnib,¹⁸ combined with its activity in a variety of pathways that have been implicated in the pathogenesis of hematologic malignancies, make it an attractive agent for use in patients with AML, MDS, chronic myelogenous leukemia (CML), and other hematologic malignancies such as multiple myeloma.

Clinical Experience With Tipifarnib

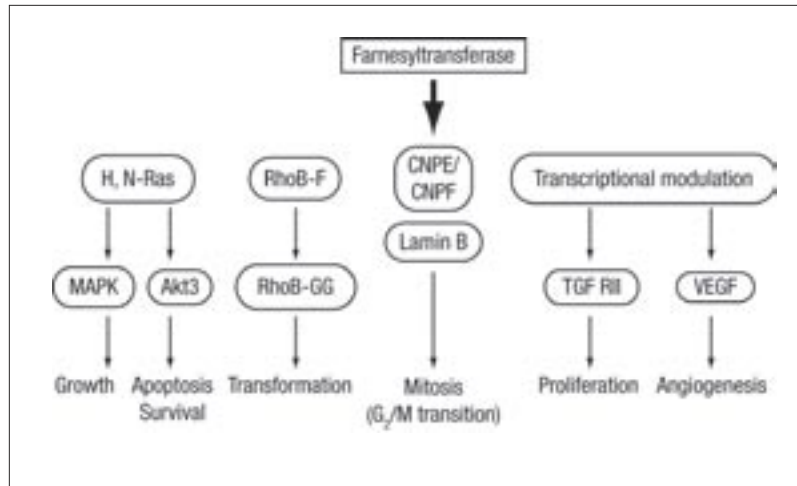
Of the FTIs currently under investigation, the largest body of clinical evidence is available for tipifarnib, primarily in hematologic malignancies (AML, MDS, CML, multiple myeloma, and others). Tipifarnib has also been evaluated in patients with various solid tumors, but the results have generally been less promising than those seen in hematologic malignancies.¹⁹

Tipifarnib in AML

Two phase I dose-escalation studies of tipifarnib have been conducted in patients with AML. In the first of these,²⁰

Figure 2. Farnesyltransferase inhibitors target multiple cellular signaling pathways.

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tipifarnib was administered orally at doses ranging from 100 mg twice daily to 1,200 mg twice daily for up to 21 days in 34 patients with poor-risk acute leukemia. A total of 25 patients had AML: 6 were newly diagnosed patients with poor-risk characteristics, 9 patients had relapsed disease, and 10 patients had disease that was refractory to either induction or reinduction therapy.

Dose-limiting toxicities occurred at the 1,200-mg twice-daily dose level, and consisted of grade 3 central nervous system toxicities: ataxia, confusion, and dysarthria. Overall, the most commonly reported non-dose-limiting toxicities (ie, grade 1 or 2) included nausea (n=9), fatigue (n=7), renal dysfunction (n=6, including 4 patients who received the 900-mg bid tipifarnib dose), and polydipsia (n=4). Treatment-induced myelosuppression occurred most commonly at the 600- and 900-mg twice-daily dose levels, with white blood cell count nadirs occurring at a median of 16 days (range, 3–22 days). Thus, the maximum tolerated dose (MTD) was determined to be 900 mg twice daily. Because pharmacodynamic studies showed that farnesyltransferase activity was consistently inhibited at twice-daily doses of 300 and 600 mg, the dose of 600 mg twice daily was selected for further evaluation. Four of the 8 patients with constitutive ERK phosphorylation at baseline had undetectable levels of phospho-ERK after one cycle of tipifarnib treatment. This finding is noteworthy because ERK is phosphorylated via the Raf-MEK pathway following Ras activation.⁷ Notably, *ras* mutations were not present in any of the 34 patients evaluated in the study, although 10 patients demonstrated complete (n=2) or partial (n=8) remissions with tipifarnib treatment, providing further evidence that tipifarnib may act upon signaling pathways other than the Ras pathway.⁷

The second dose-escalation study employed a 1-week-on/1-week-off tipifarnib administration sched-

ule.²¹ A total of 30 relapsed/refractory AML patients received oral tipifarnib at doses ranging from 400 mg twice daily to 1,600 mg twice daily using a week-on/week-off schedule and 28-day treatment cycles. Grade 3 toxicities were observed at the 400- and 1,200-mg twice-daily dose levels and included metabolic acidosis and hepatic failure in 1 patient with progressive disease and a history of hepatotoxicity with chemotherapy, and creatinine elevation in 1 patient, respectively. The maximum target treatment dose (1,600 mg bid) has been attained. Additional patients will be accrued at that dose level and the MTD will be expanded, suggesting that higher doses of tipifarnib may be administered safely using this dosing schedule. Three of 9 patients (33%) with relapsed AML who received treatment at the 1,000–1,200 mg twice-daily dose level achieved complete remission (CR).

Several phase II open-label studies have investigated the use of tipifarnib in patients with relapsed/refractory or previously untreated AML, as well as for maintenance therapy in patients with poor-risk AML in first CR. In the first of these studies, Harousseau and colleagues reported the efficacy and safety of tipifarnib in 252 patients with relapsed (n=135) or refractory (n=117) AML.¹⁴ All patients received tipifarnib 600 mg twice daily for the first 21 days of a 28-day cycle. Median treatment duration was 42 days. CRs were achieved in 11 of 252 patients (4%)—7 patients with relapsed AML and 4 patients with refractory disease. Of these 11 patients, 9 had CR, whereas 2 patients had CR with incomplete platelet recovery (CRp). The median time to response was 58 days in patients who achieved a CR and 68 days for patients who achieved CRp. Median overall survival was 369 days in patients with CR or CRp.

Myelosuppression was the major toxicity, and non-hematologic toxicities were generally mild, with grade 3

or 4 adverse events occurring in 25% of patients. Febrile neutropenia occurred in 27% of patients, and 12 infection-related deaths were reported. Thus, the investigators concluded that tipifarnib was well tolerated, with evidence of clinical activity in patients with relapsed or refractory AML.

Another open-label phase II study involved 160 elderly patients with previously untreated poor-risk AML who had either refused or were unable to tolerate conventional chemotherapeutic regimens; 4 patients with high-risk MDS and 7 patients with high-risk chronic myelomonocytic leukemia (CMML) were also enrolled in the study.²² The median patient age was 74 years (range, 34–85 years), and the majority of patients (75%) had antecedent MDS. Patients received tipifarnib 600 mg twice daily for 21 days, with a 7- to 21-day recovery period between cycles.

The overall response rate in evaluable AML patients (n=158) was 23%, with CR observed in 22 patients (14%) and partial remission (PR) or hematologic improvement (HI) in 15 patients (9%). The median duration of CR was 7.3 months, with a median overall survival of 18 months. The incidence of grade 3 or 4 nonhematologic toxicities (mostly infectious, less frequently gastrointestinal and dermatologic events) was 47%. Grade 3 or 4 neurotoxicity (primarily confusion or ataxia, frequently at the time of major infection, and reversible within 1–3 days) was observed in 8% of patients. The investigators concluded that tipifarnib was active and well tolerated in older patients with poor-risk AML, and improved survival in those who experienced a clinical response.²²

Tipifarnib has also been evaluated as post-consolidation (maintenance) therapy in patients with poor-risk AML in first CR.²³ In an open-label phase II study, 36 patients received tipifarnib 400 mg twice daily for 21 days of a 28-day cycle, up to a maximum of 16 cycles. The overall median treatment duration was 10 or more months (range, 3.5–36+ months). Nine patients completed all 16 cycles of tipifarnib and had a median CR duration of 24 months; notably, 5 of these patients remained in continuous CR after a median of 26 or more months. Another 8 patients remained in continuous CR while still receiving tipifarnib. In 15 patients, disease progression occurred while still on therapy at a median of 6.5 months. The remaining 4 patients completed fewer than 2 cycles of treatment and were excluded from the analysis.

Tipifarnib maintenance therapy was generally well tolerated. Of the 256 treatment cycles administered, hospitalization has only been required during 4 cycles: 3 for infections and 1 for bowel obstruction. Myelosuppression necessitated dose reductions in 17 of 32 patients (53%) by the third treatment cycle, and 2 patients needed

platelet transfusions. Tipifarnib treatment did not appear to have a negative effect on the efficacy of reinduction chemotherapy, as 6 of 9 patients (67%) achieved a second CR. Thus, maintenance therapy with tipifarnib is safe and well tolerated, and may prolong disease-free survival in some patients with poor-risk AML.²³

Taken together, the results of these studies warranted further investigation in patients with AML. A large, randomized, open-label, phase III study comparing tipifarnib to best supportive care (including hydroxyurea) in 457 elderly (>70 years) patients with AML who were not fit for induction chemotherapy has recently reached its primary analysis. Although 8% of patients treated with tipifarnib achieved a durable CR (with a median duration of 8 months), this did not translate into an overall survival benefit for the study population. Detailed results of this study will be published in the near future.

Tipifarnib in MDS

Four studies have investigated the safety and efficacy of tipifarnib in patients with MDS. In an initial phase I dose-escalation study, 21 patients with MDS (median age, 66 years) received tipifarnib at a starting dose of 300 mg twice daily for 21 consecutive days in a 28-day cycle.²⁴ Doses were escalated by 100 mg per day in each successive 3-patient cohort until grade 3 toxicity was observed. At this point, 3 additional patients were enrolled at that dose. If no further grade 3 toxicities were seen, the dose was escalated to the next level. Because dose-limiting toxicity (grade 3 fatigue) occurred at the 450-mg twice-daily dose, the MTD was determined to be 400 mg twice daily. Objective responses were noted in 6 of 20 patients (30%) and did not correlate with the presence of *ras* mutations, providing additional evidence that tipifarnib acts downstream of Ras.

Another phase I dose-escalation study was conducted to evaluate the use of an alternate-week dosing schedule (1 week on/1 week off) in 53 patients with MDS, only 4 of whom had *ras* mutations.²⁵ Patients received tipifarnib 100 mg twice daily to start; doses were then escalated by 100 mg twice daily until grade 2 toxicity occurred. Thereafter, the tipifarnib dose was increased by 100 mg per day until the MTD was reached. Dose-limiting toxicities (ataxia and fatigue in 1 patient each) occurred at the dose of 1,330 mg per day. Thus, the MTD appeared to be 1,200 mg per day. Responses were seen in 15 patients (29%), 3 with CRs. Notably, responses were seen even at the lowest dose level, and did not correlate with *ras* mutational status. Myelosuppression was the most common toxicity, occurring in 60% of patients, and nonhematologic toxicities included skin rash (15%), diarrhea (13%), increases in liver enzymes and bilirubin (13% and 10%, respectively), and nausea (8%).

Two phase II open-label tipifarnib studies have been completed in patients with MDS. In the first of these studies,²⁶ 28 patients received tipifarnib at a dose of 600 mg twice daily for 28 days in a 6-week cycle, a dose analogous to the results of the phase I study in advanced leukemia.²⁰ Treatment with the 600-mg twice-daily dose resulted in a high incidence of toxicities, including myelosuppression, fatigue, neurotoxicity, rash, and leg pain, and warranted treatment discontinuation in 41% of the 27 evaluable patients. A total of 3 patients had objective responses, including 2 patients with CRs. As seen in the earlier studies in AML and MDS, response was independent of *ras* mutational status.

In an attempt to improve the tolerability of tipifarnib in MDS patients, another open-label, international phase II study was conducted using a lower dose of tipifarnib in 82 patients with high-risk MDS.²⁷ Patients received tipifarnib 300 mg twice daily for 21 consecutive days every 28 days. This lower dose was associated with greater tolerability; myelosuppression was the most common treatment-related adverse event, with grade 3 or 4 neutropenia occurring in 18% of patients and grade 3 or 4 thrombocytopenia occurring in 32% of patients. Furthermore, grade 3 nonhematologic treatment-related toxicities—there were no grade 4 nonhematologic toxicities—were uncommon: rash (4%) and fatigue (2%). Twenty-six patients (32%) demonstrated responses (assessed using International Working Group 2006 criteria: 12 CR [15%] and 14 HI [17%]). Median duration of CR was 11.5 months, with 7 of 12 patients alive after at least 3 years. Of 14 patients achieving HI, 12 were monolineage (1E, 4N, 7P), 1 was bilineage (EN), and 1 was trilineage. In addition, 45% of patients demonstrated stable disease for at least 2 months (>1 year in 8 patients).

Tipifarnib in CML

Although the tyrosine kinase inhibitor imatinib (Gleevec, Novartis) is the standard of care for patients with CML, additional therapies are needed for patients who relapse or are refractory to imatinib. Although the mechanism of primary resistance to imatinib is not well understood, there is a substantial body of evidence regarding secondary (or acquired) resistance. The most common mechanism of acquired imatinib resistance involves kinase domain mutations in *BCR-ABL*, which occur in 50–90% of resistant CML cases; notably, more than 40 different mutations have been implicated in the development of resistance.²⁸ Alternatively, approximately 10% of resistant CML cases are associated with overproduction of *BCR-ABL*.²⁸ In both instances, increasing the level of kinase inhibition is thought to overcome resistance, either by increasing the dose of imatinib or by adding other agents.

In vitro studies have shown that FTIs can inhibit proliferation or induce apoptosis in imatinib-resistant tumor cell lines.^{29,30} Based on these findings, tipifarnib was evaluated as monotherapy in 22 patients with CML, 17 (77%) with imatinib-resistant disease.³¹ Patients received tipifarnib 600 mg twice daily for 4 consecutive weeks every 6 weeks. Transient CR or PR was seen in 7 patients, with a median response duration of 9 weeks. Responses appeared to be related to a decrease in vascular endothelial growth factor levels seen during treatment. Tipifarnib has also been studied in combination with imatinib in this patient population, and the results of these studies will be discussed in the section on combination tipifarnib regimens.

Tipifarnib in Multiple Myeloma and Myelofibrosis With Myeloid Metaplasia

Preclinical studies indicate that tipifarnib may be active in patients with multiple myeloma and myelofibrosis with myeloid metaplasia (MMM).³²⁻³⁴ Based on these findings, clinical studies have been conducted to investigate the use of tipifarnib in patients with each of these conditions.

The clinical experience with tipifarnib for the treatment of patients with multiple myeloma encompasses a single published phase II study in 43 patients with advanced disease.³⁵ When given orally at a dose of 300 mg twice daily for 21 of every 28 days, tipifarnib was associated with disease stabilization in 64% of patients. Interestingly, this clinical finding did not correlate with HDJ-2 farnesylation or the presence of *ras* mutations. Fatigue and anemia were the most common grade 3 or 4 toxicities, each occurring in 12.5% of patients, whereas less common grade 3 or 4 toxicities included diarrhea (8%), nausea (4%), neuropathy (8%), and thrombocytopenia (8%).

Results of a phase II study involving 34 patients with histologically confirmed MMM demonstrated that oral tipifarnib, given at a dose of 300 mg twice daily for 21 of every 28 days, produced clinically relevant improvements in 11 (33%) patients.³⁶ At study entry, all patients had symptoms of anemia (ie, hemoglobin <10 g/dL) or palpable hepatosplenomegaly. Following treatment, splenomegaly improved in 3 patients, hepatomegaly improved in 5 patients, and both splenomegaly and hepatomegaly were improved in an additional 3 patients. Across all patients with reductions in splenomegaly, a median peak reduction of 42.5% was seen in the palpable component (range, 8–100%), whereas all patients with baseline hepatomegaly had resolution of this problem at some point during therapy. Little improvement was seen in anemia; however, it should be noted that the myelosuppressive effects of tipifarnib may have masked any improvement that occurred. The promising early results seen in multiple myeloma and MMM warrant further investigation.

Tipifarnib in Non-Hodgkin Lymphoma

Patients with aggressive non-Hodgkin lymphoma (NHL) who relapse after conventional chemotherapy or stem cell transplantation have a poor prognosis, underscoring the urgent need for newer and more effective treatments in this patient population. Thus, the activity of tipifarnib was evaluated in a phase II study involving patients with relapsed aggressive NHL who received tipifarnib 300 mg twice daily for 21 of every 28 days.³⁷ Response data from a total of 42 patients with relapsed diffuse large-cell (n=37), follicular grade III (n=1), or mantle-cell (n=4) lymphoma showed that tipifarnib induced a PR in 7 of 38 evaluable patients (18%), and disease stabilization in an additional 8 patients (21%). All 7 patients with a response had diffuse large-cell histology. Overall median progression-free survival was 2 months (range, 0–25+ months), whereas progression-free survival ranged from 4.2 to 25+ months in responding patients. The primary toxicity was myelosuppression, and dose reductions were required in 33% of patients. Based on these results, the investigators concluded that tipifarnib had single-agent antitumor activity and an excellent safety profile, warranting further investigation in combination with conventional chemotherapy and other novel agents within this patient population.

Combination Tipifarnib Regimens

Based on preclinical study results showing that FTIs can inhibit proliferation or induce apoptosis in imatinib-resistant cell lines and may be synergistic in combination with imatinib,^{29,30} the combination of tipifarnib and imatinib was evaluated in two studies of patients with CML.^{38,39} In the initial dose-finding study, 23 patients with chronic phase CML were treated with escalating doses of tipifarnib plus imatinib, starting with tipifarnib 300 mg twice daily for 14 of every 21 days plus imatinib 300 mg daily, increasing to as high as tipifarnib 500 mg twice daily plus imatinib 400 mg daily.

Because dose-limiting toxicities (grade 3 fatigue and esophagitis) were observed at the highest dose level, the MTD was tipifarnib 400 mg twice daily plus imatinib 400 mg daily. Myelosuppression was the major dose-limiting toxicity, affecting a total of 6 patients (including 2 patients at the MTD level). Notably, a total of 7 of 11 evaluable patients (64%) achieved a hematologic response during treatment.³⁸

Combined tipifarnib and imatinib treatment has also been investigated in patients with advanced CML resistant to imatinib monotherapy.³⁹ A total of 12 patients were enrolled in the study, 11 patients in the accelerated phase and 1 in the blast phase. Patients received 1 of 2 dosing regimens: tipifarnib 200 mg twice daily plus imatinib 600 mg/day (n=7) or tipifarnib 300 mg twice daily plus imatinib 400 mg/day. Treatment was adminis-

tered in three cycles, with tipifarnib given on days 1–14 and imatinib given on days 1–21.

Dose-limiting toxicities included grade 3 rash and grade 3 hypokalemia in 2 patients treated at the first dose level and grade 3 syncope in 1 patient at the second dose level. Aside from these toxicities, the combination regimen was well tolerated, with grade 1 or 2 anemia and grade 1 or 2 gastrointestinal symptoms the most common hematologic and nonhematologic adverse events, respectively. Three of the 6 patients evaluable for response demonstrated complete hematologic responses (an ongoing response after 7 cycles in 1 patient in blast crisis, and ongoing responses after 9 and 16 cycles of treatment in 2 patients with accelerated phase CML). No cytogenetic responses were observed, and the study is continuing with the evaluation of additional dose-escalation cohorts.³⁹

The use of tipifarnib combination regimens has also been investigated in patients with AML/MDS. The first of these studies was a phase I study of tipifarnib plus etoposide in elderly patients with poor-risk AML who were not candidates for traditional chemotherapy regimens (N=60). Tipifarnib was administered at doses of 300, 400, or 600 mg twice daily for 14 or 21 days plus etoposide 100, 150, or 200 mg daily on days 1–3 and days 8–10, given in 28- to 63-day cycles.⁴⁰ A total of 35 enrolled patients (58%) had secondary AML, and 31 patients (52%) had adverse cytogenetics.

Toxicities were observed across all dose levels. Non-hematologic toxicities included oropharyngeal mucositis (grade ≥ 2 in 15% of patients), neurotoxicity (30% overall, grade ≥ 2 in 20% of patients), renal impairment (6%), hyperbilirubinemia (6%), rash (20%), and fatigue (20%). Twelve of 56 evaluable patients (21%) achieved CR, with a median duration of 7+ months. An additional 11 patients (20%) achieved PR or hematologic improvement. Based on these results, it may be concluded that this oral regimen is feasible on an outpatient basis for elderly patients with newly diagnosed AML who are not candidates for traditional cytotoxic chemotherapy.

Tipifarnib was also evaluated in combination with standard idarubicin and cytarabine therapy in a phase I/II study in 74 patients with newly diagnosed AML or high-risk MDS.⁴¹ Patients received induction therapy with idarubicin IV 12 mg/m² per day on days 1–3, cytarabine 1.5 g/m² over 24 hours on days 1–4 (days 1–3 only if age 60 years or older), and tipifarnib 200 to 300 mg twice daily for 21 consecutive days every 28-day cycle. Patients who achieved CR then received 5 courses of consolidation therapy with idarubicin IV 8 mg/m² per day on days 1–3, cytarabine 0.75 g/m² over 24 hours on days 1–4 (days 1–3 only if age 60 years or older), and tipifarnib 300 mg twice daily for 14 consecutive days every 4–6 weeks. Maintenance therapy consisted of tipifarnib 300 mg twice daily

for 21 consecutive days every 4–6 weeks for an additional 6 months.

CR was achieved in 48 patients (65%), and 9 additional patients (12%) achieved CRp. After a median 22 weeks of follow-up, 34 patients remained on study, 9 patients relapsed, and 2 patients died of causes unrelated to treatment while in CR. The most common grade 3 adverse events were transient diarrhea in 31 patients (42%) and hyperbilirubinemia in 10 patients (14%). The investigators concluded that this combination of idarubicin, cytarabine, and tipifarnib resulted in a high rate of CR in patients with AML, but with an increased incidence of diarrhea and hyperbilirubinemia.⁴¹

Most recently, tipifarnib in combination with low-dose cytarabine (LDAC) has been evaluated in a phase I study of 57 patients with high-risk MDS or AML.⁴² Patients with MDS (IPSS Int 1 or high) or untreated or relapsed/refractory AML received escalating doses of tipifarnib orally twice daily for 21 of every 28 days and LDAC subcutaneously twice daily for 10 of every 28 days. Interim results demonstrated a MTD of tipifarnib 300 mg orally twice daily every 21 days and LDAC 15 mg subcutaneously twice daily every 10 days of a 2-day cycle.

Predictors of Response to Tipifarnib

In an attempt to identify factors predictive of a response to tipifarnib treatment, Raponi and colleagues examined gene expression in patients from an open-label phase II study in relapsed (n=135) and refractory (n=117) AML.^{14,43,44} Nineteen top genes were identified that predicted response to tipifarnib. Of these, the *AKAP13* gene was the most robust for the identification of nonresponders to tipifarnib.⁴³ The predictive value of *AKAP13* provided a sensitivity of 93% in identifying responders and a specificity of 61%, resulting in an overall diagnostic accuracy of 69%. Clinically, tipifarnib responders demonstrated low levels of *AKAP13* and *IL3RA*, whereas nonresponders demonstrated the opposite gene expression profile. Furthermore, a three-gene sequence was found to correlate with survival, and responders with this genetic sequence had significantly improved survival compared with nonresponders ($P=.017$).

To date, efforts to correlate *ras* mutational status with treatment response have proven unsuccessful. As noted previously, early studies in adults with leukemia and MDS showed no correlation between the presence of *ras* mutations and the response to tipifarnib.^{7,24,25} These results are supported by the results of a study conducted by Goemans and colleagues in pediatric AML showing no difference in tipifarnib sensitivity between patients with or without *ras* mutations.⁴⁵ Thus, it appears that tipifarnib

may exert its effects on other farnesylated proteins downstream of Ras.

Summary and Conclusions

Based on the clinical experience to date, tipifarnib may be a promising agent for the treatment of hematologic malignancies. However, the precise mechanism of action of FTIs requires further investigation. It appears that their antitumor effects are independent of *ras* mutational status, suggesting possible effects on downstream cellular pathways. Because hematologic malignancies are likely driven by multiple genetic aberrations, the most effective treatment strategy will probably combine multiple agents with complementary mechanisms of action. Thus, additional studies of combination regimens that incorporate tipifarnib with other agents used in the treatment of hematologic malignancies are crucial. Early results from studies combining tipifarnib with imatinib or etoposide have been promising, and warrant further evaluation in larger clinical trials.

References

1. Boguski MS, McCormick F. Proteins regulating Ras and its relatives. *Nature*. 1993;366:643-654.
2. End DW. Farnesyl protein transferase inhibitors and other therapies targeting the Ras signal transduction pathway. *Invest New Drugs*. 1999;17:241-258.
3. End DW, Mevellec L, Angibaud P. Farnesyl protein transferase inhibitors: molecular mechanisms and progress in the clinic. *Curr Top Med Chem*. [In press.]
4. Khosravi-Far R, Cox AD, Kato K, Der CJ. Protein prenylation: key to ras function and cancer intervention? *Cell Growth Differ*. 1992;3:461-469.
5. Rowinsky EK, Windle JJ, Von Hoff DD. Ras protein farnesyltransferase: a strategic target for anticancer therapeutic development. *J Clin Oncol*. 1999;17:3631-3652.
6. Reuter CWM, Morgan MA, Bergmann L. Targeting the Ras signaling pathway: a rational, mechanism-based treatment for hematologic malignancies? *Blood*. 2000;96:1655-1669.
7. Karp JE. Farnesyl protein transferase inhibitors as targeted therapies for hematologic malignancies. *Semin Hematol*. 2001;38(3 suppl 7):16-23.
8. Sebti SM, Hamilton AD. Farnesyltransferase and geranylgeranyltransferase I inhibitors in cancer therapy: important mechanistic and bench to bedside issues. *Expert Opin Investig Drugs*. 2000;9:2767-2782.
9. Du W, Prendergast GC. Geranylgeranylated RhoB mediates suppression of human tumor cell growth by farnesyltransferase inhibitors. *Cancer Res*. 1999;59:5492-5496.
10. Klippel A, Escobedo MA, Wachowicz MS, et al. Activation of phosphatidylinositol 3-kinase is sufficient for cell cycle entry and promotes cellular changes characteristic of oncogenic transformation. *Mol Cell Biol*. 1998;18:5699-5711.
11. Lancet JE, Karp JE. Farnesyltransferase inhibitors in hematologic malignancies: new horizons in therapy. *Blood*. 2003;102:3880-3889.
12. Prendergast GC, Oliff A. Farnesyltransferase inhibitors: antineoplastic properties, mechanisms of action, and clinical prospects. *Semin Cancer Biol*. 2000;10:443-452.
13. Harousseau JL. Farnesyltransferase inhibitors in hematologic malignancies. *Blood Rev*. 2007;21:173-182.
14. Harousseau JL, Lancet JE, Reiffers J, et al. A phase 2 study of the oral farnesyltransferase inhibitor tipifarnib in patients with refractory or relapsed acute myeloid leukemia. *Blood*. 2007;109:5151-5156.
15. Raponi M, Harousseau JL, Lancet JE, et al. Identification of molecular predictors of response in a study of tipifarnib treatment in relapsed and refractory acute myelogenous leukemia. *Clin Cancer Res*. 2007;13:2254-2260.

16. Ashar HR, James L, Gray K, et al. Farnesyl transferase inhibitors block the farnesylation of CENP-E and CENP-F and alter the association of CENP-E with the microtubules. *J Biol Chem*. 2000;275:30451-30457.
17. Crespo NC, Ohkanda J, Yen TJ, Hamilton AD, Sebti SM. The farnesyltransferase inhibitor, FTI-2153, blocks bipolar spindle formation and chromosome alignment and causes prometaphase accumulation during mitosis of human lung cancer cells. *J Biol Chem*. 2001;276:16161-16167.
18. Zujewski J, Horak ID, Bol CJ, et al. Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. *J Clin Oncol*. 2000;18:927-941.
19. Sebti SM, Adjei AA. Farnesyltransferase inhibitors. *Semin Oncol*. 2004;31(1 suppl 1):28-39.
20. Karp JE, Lancet JE, Kaufmann SH, et al. Clinical and biologic activity of the farnesyltransferase inhibitor R115777 in adults with refractory and relapsed acute leukemias: a phase I clinical-laboratory correlative trial. *Blood*. 2001;97:3361-3369.
21. Kirschbaum M, Selwyn Stein A, Tuscano J, et al. A phase I study of the farnesyltransferase inhibitor tipifarnib in a week-on week-off dose schedule in acute myelogenous leukemia. *Blood*. 2006;108:551a. Abstract 1948.
22. Lancet JE, Gojo I, Godlib J, et al. A phase 2 study of the farnesyltransferase inhibitor tipifarnib in poor-risk and elderly patients with previously untreated acute myelogenous leukemia. *Blood*. 2007;109:1387-1394.
23. Karp JE, Smith BD, Gojo I, et al. Phase II trial of the oral farnesyltransferase inhibitor tipifarnib as maintenance therapy in first complete remission in adults with acute myelogenous leukemia and poor risk features. *Clin Cancer Res*. [In press.]
24. Kurzrock R, Kantarjian HM, Cortes JE, et al. Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase I setting. *Blood*. 2003;102:4527-4534.
25. Kurzrock R, Verstovsek S, Wright JJ, et al. Phase I study using alternate week administration of the farnesyl transferase inhibitor R115777 (Zarnestra) in patients with myelodysplastic syndrome. *Blood*. 2004;104(pt 1):402a. Abstract 1436.
26. Kurzrock R, Albitar M, Cortes JE, et al. Phase II study of R115777, a farnesyl transferase inhibitor, in myelodysplastic syndrome. *J Clin Oncol*. 2004;22:1287-1292.
27. Fenaux P, Raza A, Mufti GJ, et al. A multicenter phase 2 study of the farnesyltransferase inhibitor tipifarnib in intermediate- to high-risk myelodysplastic syndrome. *Blood*. 2007;109:4158-4163.
28. Shah NP. Loss of response to imatinib: mechanisms and management. *Hematology Am Soc Hematol Educ Program*. 2005;183-187.
29. Hoover RR, Mahon FX, Melo JV, Daley GQ. Overcoming STI571 resistance with the farnesyl transferase inhibitor SCH66336. *Blood*. 2002;100:1068-1071.
30. Nakajima A, Tauchi T, Ohyashiki K. ABL-specific tyrosine kinase inhibitor, STI571 in vitro, affects Ph-positive acute lymphoblastic leukemia and chronic myelogenous leukemia in blastic crisis. *Leukemia*. 2001;15:989-990.
31. Cortes J, Albitar M, Thomas D, et al. Efficacy of the farnesyl transferase inhibitor R115777 in chronic myeloid leukemia and other hematologic malignancies. *Blood*. 2003;101:1692-1697.
32. Beupre DM, Cepero E, Obeng EA, Boise LH, Lichtenheld MG. R115777 induces Ras-independent apoptosis of myeloma cells via multiple intrinsic pathways. *Mol Cancer Ther*. 2004;3:179-186.
33. Bolick SC, Landowski TH, Boulware D, et al. The farnesyl transferase inhibitor, FTI-277, inhibits growth and induces apoptosis in drug-resistant myeloma tumor cells. *Leukemia*. 2003;17:451-457.
34. Mesa RA, Tefferi A, Gray LA, Reeder T, Schroeder G, Kaufmann SH. In vitro antiproliferative activity of the farnesyltransferase inhibitor R115777 in hematopoietic progenitors from patients with myelofibrosis with myeloid metaplasia. *Leukemia*. 2003;17:849-855.
35. Alsina M, Fonseca R, Wilson EF, et al. Farnesyltransferase inhibitor tipifarnib is well tolerated, induces stabilization of disease, and inhibits farnesylation and oncogenic/tumor survival pathways in patients with advanced multiple myeloma. *Blood*. 2004;103:3271-3277.
36. Mesa RA, Camoriano JK, Geyer SM, et al. A phase 2 consortium (P2C) trial of R115777 (tipifarnib) in myelofibrosis with myeloid metaplasia. *Blood*. 2004;104(pt 1):422a. Abstract 1509.
37. Witzig TE, Maurer MJ, Johnston PB, et al. Oral tipifarnib (R115777) has single agent anti-tumor activity in patients with relapsed aggressive non-Hodgkin lymphoma (NHL): results of a phase II trial in the University of Iowa/Mayo Clinic Lymphoma SPORE (CA97274). *Blood*. 2006;108. Abstract 530.
38. Cortes J, Garcia-Manero G, O'Brien S, et al. A phase I study of tipifarnib in combination with imatinib mesylate (IM) for patients (Pts) with chronic myeloid leukemia (CML) in chronic phase (CP) who failed IM therapy. *Blood*. 2004;104(pt 1):176. Abstract 1011.
39. Godlib J, Mauro M, O'Dwyer ME, et al. Tipifarnib (ZARNESTRA) and Imatinib (GLEEVEC) combination therapy in patients with advanced chronic myelogenous leukemia (CML): preliminary results of a phase I study. *Blood*. 2003;102:909a. Abstract 3384.
40. Karp JE, Feldman EJ, Morris L. Active oral regimen for elderly adults with newly diagnosed acute myelogenous leukemia (AML): phase I trial of oral tipifarnib (T) combined with oral etoposide (E) for adults age 70 who are not candidates for traditional cytotoxic chemotherapy (TCC). *Blood*. 2006;106. Abstract 426.
41. Alvarez RH, Kantarjian H, Garcia-Manero G, et al. Farnesyl transferase inhibitor (tipifarnib, Zarnestra; Z) in combination with standard chemotherapy with idarubicin (IDA) and cytarabine (ara-C) for patients (pts) with newly diagnosed acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). *Blood*. 2006;106:565a-566a. Abstract 1999.
42. Cortes JE, Feldman EJ, Douer D, Raza A, Fruchtmann S. Phase I evaluation of tipifarnib in combination with low-dose Ara-C (LDAC) in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML): interim results. *J Clin Oncol*. 2007;25:Abstract 14014.
43. Raponi M, Harousseau JL, Lancet JE, et al. Identification of molecular predictors of response in a study of tipifarnib treatment in relapsed and refractory acute myelogenous leukemia. *Clin Cancer Res*. 2007;13:2254-2260.
44. Raponi M, Lancet JE, Fan H, et al. A two gene classifier for predicting response to the farnesyltransferase inhibitor tipifarnib in acute myeloid leukemia. *Blood*. 2008;111:2589-2596.
45. Goemans BF, Zwaan CM, Harlow A, et al. In vitro profiling of the sensitivity of pediatric leukemia cells to tipifarnib: identification of T-cell ALL and FAB M5 AML as the most sensitive subsets. *Blood*. 2005;106:3532-3537.