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Suppression of Farnesyltransferase Activity in Acute Myeloid Leukemia and Myelodysplastic Syndrome: Current Understanding and Recommended Use of Tipifarnib

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Abstract

Importance of the field—Acute Myeloid Leukemia (AML) and myelodysplastic syndrome (MDS) incidence in the United States increase with age. Given the progressive aging of the general population, incidence of these diseases is likely to continue to rise in the future. There is an earnest need for therapeutic developments because of the poor prognosis of these diseases. Since the knowledge of molecular genetics in AML and MDS has expanded recently, targeted therapeutics should offer an exciting new frontier for advancement. Of all the targeted inhibitors developed, tipifarnib represents one of the few compounds with some activity as a single agent.

Areas to be covered in this review—Described in this review are the molecular targets of tipifarnib, safety and tolerability of the drug, chemistry, and clinical efficacy in AML.

What the reader will gain—The reader will gain a thorough understanding of tipifarnib as it relates to the current and future use of the drug in AML.

Take home message—The future of tipifarnib, along with other molecularly-targeted drugs, lies in achieving a better understanding of leukemia biology and harnessing the activity of this agent using predictive biomarkers for improved patient selection.

Keywords

Acute myeloid leukemia; myelodysplastic syndrome; Ras; farnesyltransferase; treatment; lipid

2.5 Introduction

2.5.1 Disease Incidence and Prevalence

Acute Myeloid Leukemia (AML) incidence in the United States was assessed from 1973–1998 by the Surveillance, Epidemiology, and End Results (SEER) program(Xie, Davies et al. 2003). Results of incidence and 5-year survival were based on nine reporting areas and the specific rates for age (birth–19, 20–44, 45–64, and 65 + years), gender, and race (black, white) were examined. Each year, a total of 18,717 cases of AML were identified with the highest incidence in individuals over 65 years of age (incidence rate of 150 per million based on 1970 US standards). The incidence of AML in children (birth to 19 years of age) was 1,187 cases per million. The 5 and 10 year survival rates in this study, among the various age groups, were calculated for patients with all types of leukemia including AML, acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphoblastic leukemia (CLL). Patients with AML had the worst prognosis among all types

of leukemia with 5-year survival rates of 22% (birth-19 years), 13.83% (22–44 years), 6.52% (45–64 years), and 2.49% (over 65 years old) (Xie, Davies et al. 2003). About half of older AML patients have adverse prognostic features at diagnosis, i.e. unfavorable cytogenetics and/or AML arising after MDS. These patients are less responsive and less tolerant to conventional chemotherapy and are potential candidates for experimental approaches as first line therapy. An active oral therapy, such as tipifarnib, could offer therapeutic opportunity to frail patients.

Myelodysplastic syndromes (MDS) are characterized by incompetent hematopoiesis that leads to single or multi-lineage peripheral cytopenias with the development of AML in approximately 30–40% of cases (Greenberg, Young et al. 2002). The etiology of MDS is unknown and the factors leading to AML progression are not well characterized. Registration of MDS to population-based cancer registries in the United States was initiated in 2001 and results were recently reported (Ma, Does et al. 2007; Rollison, Howlader et al. 2008). Data from the North American Association of Central Cancer Registries (NAACCR) and SEER programs, encompassing 82% of the US population estimated that the average case numbers for the entire United States, based on more than 40,000 observations, was 3.3 per 100,000 annually for 2001 through 2003 (Rollison, Howlader et al. 2008). Incidence rates increased with age ($P < .05$) and were highest among whites and non-Hispanics. (Rollison, Howlader et al. 2008). The incidence of both AML and MDS is expected to further increase in the years to come, given the progressive aging of the general population.

2.5.2 Unmet medical needs

There is a serious unmet medical need for the discovery of new pharmaceutical or biological therapies with disease remitting activity that target the molecular and cellular abnormalities that drive clonal expansion and survival of leukemic cells. Available data suggest that pharmacological modulators of signal transduction pathways hold promise and may ultimately lead to improved outcome for AML patients. None of these agents as single therapy, however, has shown significant activity possibly due to the complexity of signaling events and disease heterogeneity. Signaling molecules that have been targets in AML include FLT3 (Mattison, Ostler et al. 2007; Pinheiro, de Sa Moreira et al. 2008), Ras/Raf/MAPK (Padua, Carter et al. 1988; Ehmann, Horn et al. 2006), mTOR (Recher, Dos Santos et al. 2005), KIT (Faderl, Pal et al. 2009), and VEGF (Dickson and Shami 2001). Of all the targeted inhibitors tested, tipifarnib represents one of the few compounds with single agent activity in individuals with both AML and MDS (Lancet and Karp 2003). In this review, information will be provided about the molecular targets of tipifarnib and the future of this agent for the treatment of AML.

2.6 Body of the Review

2.6.1 Farnesyltransferase inhibitors as molecular bullets

Mutations of RAS genes, or activation of RAS in the absence of mutations, occurs in high frequency in MDS and AML suggesting that targeted disruption of this important signaling molecule may be used therapeutically (Saglio, Serra et al. 1989; Auewarakul, Lauhakirti et al. 2006; Bacher, Haferlach et al. 2006; Ehmann, Horn et al. 2006; Niimi, Harada et al. 2006). Leukemic cells from roughly 10–40% of MDS cases and 15–25% of AML cases have been reported to have RAS mutations (Padua, Carter et al. 1988; Paquette, Landaw et al. 1993; Neubauer, Greenberg et al. 1994; Padua and West 2000; Reuter, Morgan et al. 2000).

RAS is a small farnesylated, GTPase that is critical for many receptor-mediated pathways leading to MEK/ERK activation. (Li, Batzer et al. 1993) Inactive Ras binds GDP but when activated, GDP is exchanged for GTP enabling Ras to bind Raf-1 and signal to downstream

intermediates.(de Rooij and Bos 1997) The mechanism of this activation is dependent on the NH2-terminal domain of Raf-1 known as the Ras-binding domain (RBD) that reversibly interacts with Ras in the plasma membrane (pathway shown diagrammatically in Figure 1). (de Rooij and Bos 1997)

The farnesyl group on Ras is necessary for movement from the cytoplasm to the plasma membrane and for membrane anchorage; a process that is essential for activation.(de Rooij and Bos 1997) Farnesyltransferase is the enzyme that catalyses the transfer of a 15-carbon isoprenyl farnesyl moiety to the carboxy terminus of RAS and other proteins containing the peptide target sequence “CAAX, often referred to as a CAAX-box”. A related enzyme, geranylgeranyl transferase I (GGT-1) catalyzes the addition of a 20-carbon geranylgeranyl group to CAAX-containing proteins. The “X” residue determines the specificity of these two enzymes.(Basso, Kirschmeier et al. 2006) Under physiologic conditions, the specificities of these enzymes are relatively well maintained. Targeted disruption of FTase activity leads to the inactivation of RAS function.(Agrawal and Somani 2009).

2.6.2 Introduction to the compound

Farnesyltransferase inhibitors (FTIs) represent an effective method to disrupt RAS function by blocking its ability to anchor to the plasma membrane, causing a GDP-locked, inactive state.(Lerner, Qian et al. 1995; Lerner, Zhang et al. 1997; Bolick, Landowski et al. 2003; Santucci, Mackley et al. 2003) Different FTIs have been synthesized and shown to have both *in vitro* and *in vivo* activity in cell lines or animal models, respectively(Tamanoi 1993; Sebti and Hamilton 1996). Several FTIs have entered clinical trials, beginning with dose and schedule optimization and identification of toxicities. Tipifarnib (initially R115777) is a very potent and highly selective inhibitor of farnesyltransferase (FTase) that was first developed in April 1997.(Norman 2002) Although the drug is highly selective for FTase, a plethora of activities result from the numerous cellular proteins that require farnesylation for activity. Tipifarnib inhibited proliferation of several cell lines with both mutated and non-mutated RAS.(Mesa, Tefferi et al. 2003) In most cell types, repressed proliferation was not accompanied by the induction of cell death suggesting that the drug has cytostatic rather than cytotoxic activity. Tipifarnib-induced apoptosis was observed, however, in both multiple myeloma cell lines and in primary cultures from patients with multiple myeloma suggesting that the drug is capable of inducing apoptosis in some neoplastic cell lineages other than AML.(Le Gouill, Pellat-Deceunynck et al. 2002; Cortes, Albitar et al. 2003; Ochiai, Uchida et al. 2003; Alsina, Fonseca et al. 2004) Evidence clearly shows that the mechanism of action is cell-type dependent and includes inhibition of angiogenesis, induction of apoptosis, and antiproliferative effects.

Prenylation catalyzed by geranylgeranyltransferase type 1 is not sensitive to suppression by tipifarnib. GGTase plays an important role in resistance to tipifarnib and other FTIs since selective inhibition of farnesylation often leads to a compensatory increase in geranylgeranylation that restores membrane anchor-associated activation and cellular function (Mor et al. 2007).

There have been no data that clearly link suppression of Ras with clinical response to tipifarnib. This may be due to the pleiotrophic effects of the drug against other farnesylated cellular targets(Basso, Kirschmeier et al. 2006). Many targets of FTIs have been described and some are likely to be undefined. A list of the known farnesylated proteins inhibited by tipifarnib is provided in Table 1. A better understanding of leukemia biology and the molecular targets of tipifarnib is needed to fully understand the mechanism of action of this drug and more effectively apply it to select patients with AML.

2.6.3 Chemistry

Tipifarnib is a methyl-quinolinone derivative (molecular formula $C_{27}H_{22}C_{12}N_4O$) that acts as a potent and selective nonpeptidomimetic inhibitor of farnesyl transferase protein (FTP) both *in vitro* and *in vivo* (Norman 2002). Tipifarnib is supplied as 100 mg (white, in boxes of 126 tablets each) circular film-coated tablets. Tablets should be protected from moisture and stored at room temperature (15–25°C, 59–77°F) with stability at least 36 months. Tablet bioavailability increases with a meal so the drug should be administered with food.

2.6.4 Pharmacodynamics

Competitive inhibition of farnesyltransferase enzyme activity, using K-Ras peptide as a substrate, occurred with an IC_{50} of 7.9 nM. (End et al. 2001) Forty of 53 (75%) human tumor cell lines were found to be sensitive to tipifarnib *in vitro* and most of these sensitive cell lines carried H-RAS or N-RAS mutations. In contrast, fifty percent of tumor cell lines displaying mutant K-ras genes were resistant or required higher concentrations for growth inhibition. Oral administration of tipifarnib in xenograft models carrying mutant H-RAS and K-RAS revealed that twice daily doses with 6.25–100 mg/kg inhibited tumor growth *in vivo* (End et al. 2001). The ratio of unfarnesylated and farnesylated HDJ2, a farnesylated chaperone protein with unknown biological function, in peripheral blood mononuclear cells is accepted as the best marker of pharmacological efficacy and pharmacodynamics (Karp, Lancet et al. 2001).

2.6.5 Pharmacokinetics and metabolism

Pharmacokinetic studies were performed with tipifarnib and revealed a linear relationship between dose and maximum plasma concentration (Karp, Lancet et al. 2001; Patnaik et al. 2003). There was also a linear relationship between the dose and area under the curve over 12 hours at all dosage levels (Karp, Lancet et al. 2001). In individuals with AML, weekly marrow samples demonstrated a dose-dependent accumulation of tipifarnib in bone marrow with large increases in concentration occurring at 600 mg twice daily. Tipifarnib is currently available as a tablet and the bioavailability of tablets was compared to a capsule formulation, in patients with solid tumors but not in AML (Crul, de Klerk et al. 2002). The investigators used tipifarnib administered once daily in doses of 300 or 400 mg. Blood samples were drawn up to 24 hours after drug administration, and the plasma levels were measured using high performance liquid chromatography (HPLC) (Crul, de Klerk et al. 2002). The pharmacokinetic parameters examined included time to maximal plasma concentration (T_{max}), half-life ($t_{1/2}$), maximal plasma concentration (C_{max}) and area under the curve at twenty-four hours (AUC_{24h}). The point estimates of the log-normalized C_{max} and AUC_{24h} were 0.94 and 0.92, respectively (0.81–1.09 and 0.83–1.03 90% CI) (Crul, de Klerk et al. 2002).

2.6.6 Clinical efficacy

2.6.6.1 Phase I studies—One of the earliest phase I trials of poor-risk acute leukemias revealed that tipifarnib was associated with a clinical response in 10 (29%) of the 34 evaluable patients, including 2 complete remissions (Karp, Lancet et al. 2001). This promising response rate, as a single agent in poor risk leukemias, produced excitement over the potential of tipifarnib for the treatment of AML (Karp, Lancet et al. 2001). Cohorts of patients received tipifarnib at doses ranging from 100 mg twice daily (bid) up to 1200 mg bid for up to 21 days. Dose-limiting toxicity was observed at 1200 mg bid (Karp, Lancet et al. 2001). Central neurotoxicity, including ataxia, confusion, and dysarthria, proved to be the dose-limiting toxicity. Non-dose-limiting toxicities included myelosuppression, nausea, paresthesias, renal insufficiency, polydipsia (Cortes, Albitar et al. 2003). *In vivo*, 300 mg bid actively suppressed farnesylation of lamin A and HDJ-2. Genetic analyses of mutation status

failed to reveal a linkage between N-RAS mutations and clinical response. Comparison of peripheral blood samples obtained before and after treatment showed that phosphorylated ERK, an effector molecule that is downstream of Ras-mediated signaling, was reduced in roughly 50% of patients after one cycle of treatment. Tipifarnib clinical response failed to correlate with the presence of mutant RAS and other biomarkers examined, which has been an enigma that has vexed the scientific community throughout the clinical development as single agent therapy for AML in Phase II and Phase III studies.

Due to the modest activity as a single agent, the efficacy of tipifarnib combinations was examined in preclinical and phase I studies (Karp, Flatten et al. 2009). Synergistic activity was observed when an AML cell line (HL-60) and primary cells from AML patients were treated with tipifarnib in combination with the topoisomerase II inhibitor etoposide. Tipifarnib increased the amount of apoptosis induced by etoposide and reduced the number of colonies present in colony formation assays after 10–14 days. The mechanism for the synergistic activity was explored and found to be through inhibition of the ribosomal S6 protein phosphorylation and p70 S6 kinase 1, which is consistent with a combined effect on mTOR signaling. Results of these preclinical studies led to a phase I clinical trial to examine the tolerability and efficacy of tipifarnib and etoposide combination therapy in AML patients. A total of 101 patients were evaluated for eligibility and 84 were enrolled and treated with a 14- or 21-day course of tipifarnib at a dose of either 600 or 400 mg. The dose of etoposide was either 100 or 200 mg. In vivo, the investigators explored whether tipifarnib plus etoposide decreased ribosomal S6 phosphorylation. Of the 84 patients enrolled, 21 patients (84%) achieved a complete response. Using a poynomia model to estimate the relationship between the therapeutic dose of the drug combination and response, the response tended to be higher in patients who received a higher dose of both drugs (tipifarnib 600mg twice daily for 14-days plus etoposide dose 150 mg daily on days 1–3 and 8–10 or 400 mg twice daily tipifarnib for 14-days in combination with 200 mg daily etoposide on days 1–3 and 8–10).

An additional phase I study investigated the use of tipifarnib in combination with standard dose and schedule of daurorubine/cytarabine induction therapy (Brandwein et al, 2009) of AML in patients age 60 years and over. Tipifarnib was dose evaluated over four levels (200, 300, 400, and 600 mg po bid) in days six to 15. In this study, there were no dose-limiting toxicities due to delayed hematologic recovery. The regimen was well tolerated and the maximum tolerated dose was not reached. The investigators recommended that the 600 mg bid dose of tipifarnib be considered for further study in this combination regimen. Despite these promising trials, failure to identify the precise mechanism of action of tipifarnib for leukemia therapy has been problematic but has engendered further investigations to uncover the basic mechanisms of leukemogenesis.

2.6.6.2 Phase II studies—Successful enzyme target inhibition, low toxicity, and promising response rates, prompted further investigation of tipifarnib in phase II trials. These trials focused on clarifying the response rate and identifying the downstream signal transduction targets that may be modified by these agents in order to understand a precise molecule linkage to response. It was anticipated that this information would generate optimal use of FTIs in patients with AML and lead to the development of more successful combination. A summary of Phase I, II and III trials is shown in Table 2. (Harousseau, Lancet et al. 2007; Karp, Lancet et al, 2001; Harousseau, Martinelli et al. 2009; Kirschbaum et al, 2007; Karp, Flatten et al, 2009; Brandwein et al, 2009; Lancet et al, 2007; Erba et al, 2007; Karp, Smith et al, 2008)

After completion of several Phase II trials, it was obvious that tipifarnib failed to demonstrated significant responses in unselected AML patients despite obvious activity in

the initial trials. Therefore, the attention then turned to better understanding the molecular mechanism of the drug starting with investigations to identify baseline predictive markers associated with response. Recent gene expression profiles from the bone marrow of patients from a phase 2 study of the FTI tipifarnib in older adults with AML revealed that the ratio of *RASGRP1/APTX* gene expression prior to treatment displayed high fidelity and excellent accuracy as a predictive marker of response (Raponi, Lancet et al. 2008). *RASGRP1* is a guanine nucleotide exchange factor involved in the activation of RAS, and the *APTX* (apratatin) gene product is involved in DNA excision repair (Gueven, Becherel et al. 2004). In addition to predicting response, the classifier also proved to be an independent predictor of improved overall survival (154 vs 56 days; $P < .001$). For use of tipifarnib in combination and as a single agent in AML, this molecular signature warrants further validation in a prospective study.

2.6.6.3 Phase III trial—Due to the tolerability, efficacy of tipifarnib, and the unmet need for therapy in elderly AML, tipifarnib was investigated for the treatment of older patients not eligible for transplantation. This phase 3 trial was conducted as first-line therapy in patients ≥ 70 years old with newly diagnosed, de novo, or secondary AML (Harousseau, Martinelli et al. 2009). In this open-label study, the efficacy and safety of tipifarnib was compared with best supportive care (BSC), including hydroxyurea. Tipifarnib was administered at a dose of 600 mg orally twice daily for 21 out of a 28-day cycle. The primary endpoint was overall survival. A total of 457 patients enrolled, with 24% of the patients being 80 years of age or older. The median survival was 107 days for the tipifarnib arm and 109 days for the BSC arm. The hazard ratio (tipifarnib vs BSC) for overall survival was 1.02 (P value by stratified log-rank test, .843). The complete response rate for tipifarnib was lower in this study (8%) compared to previous Phase II studies. Cytopenias were the most frequently observed grade 3 or 4 adverse events. Therefore, the conclusion from this randomized study was that tipifarnib treatment, in this patient population, was not better than standard of care.

2.6.7 Safety and tolerability

2.6.7.1 Animal Studies—Cataracts were noted in preclinical toxicology studies only. Cataracts were noted in Wistar rats treated by oral gavage in repeated dose toxicity studies for 3 months at doses of 40 and 60 mg/kg (product literature). Rats treated for 7 weeks by oral gavage at 60 mg/kg also apparently developed cataracts. Cataracts were not noted in Wistar rats treated by continuous intravenous infusion for two weeks at daily doses of 12, 24 and 48 mg/kg. Cataracts were not noted in extensive preclinical toxicology studies performed in beagle dogs and rabbits.

2.6.7.2 Reported Adverse Events and Potential Risks in Humans—Safety observations from single agent clinical studies have been combined ($n=726$). These consist of Phase 1, Phase 2, and Phase 3 studies, with various dosing regimens in both adults and children with various types of cancers (Schellens et al, 2001; Punt et al, 2000; Horak et al 2000; Richards, Thibault et al, 2003; Van de Velde et al, 2003; Richards, De Porre et al, 2002 OK; Howes et al, 2003; Palmer, Kerstens et al, 2003). The most frequently reported adverse events are general symptoms (body as a whole including fatigue, fever, asthenia, pain, back pain, peripheral edema, chest pain, edema, rigors, and leg pain) or gastrointestinal symptoms. The overall incidence of these adverse events is similar between participants receiving tipifarnib compared to placebo (Howes et al, 2003).

The most frequently reported drug related adverse events are associated with myelosuppression: granulocytopenia (23%), thrombocytopenia (23%), anemia (21%), and leukopenia (12%). Drug-related adverse events were considered by the investigator to be

possibly, probably, or very likely associated with the administration of tipifarnib.(Palmer, Thibault et al, 2003) The most common signs of myelosuppression, reported as adverse events in $\geq 10\%$ of treated participants, were anemia (39%), thrombocytopenia (32%), granulocytopenia (29%), and leukopenia (12%). Almost all of these events occurred at doses of 300 mg bid and above, and the majority of these events were grade 3 and 4 (NCI-CTC version 2.0).

Other major adverse events reported included fatigue, asthenia, lethargy, and malaise. Less frequently reported adverse events included photosensitivity, rash/desquamation, anorexia, diarrhea, nausea, vomiting, and elevated lipase. An adverse event more frequently occurring in AML included febrile neutropenia, more specifically fever of unknown origin without clinically or microbiologically documented infection ($ANC < 1.0 \times 10^9/L$, fever $\geq 38.5^\circ C$) and infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils ($ANC < 1.0 \times 10^9/L$).

Electrolyte abnormalities occurred rarely and included hyopkalemia, which was reported as an adverse event in 5% of participants receiving tipifarnib at 300 mg bid and 38% of participants receiving doses above 300mg bid. Investigators considered hypokalemia to be drug-related in 0.8% of cases at 300 mg bid (no Grade 3 or 4) and 10.5% of cases at higher doses (4.2% Grade 3 or 4). The majority of the latter occurred in participants with AML receiving 600 mg bid, a large proportion of whom were also receiving concomitant diuretics or amphotericin B.

The most serious non-hematological toxicity reported in early studies was mood alteration, motor neuropathy, and sensory neuropathy. Neurotoxicity was observed predominantly in participants receiving continuous daily dosing of tipifarnib at 300 mg bid. or above. Neurotoxicity has been operationally defined as any incidence of paresthesia, peripheral neuropathy, hypoesthesia, and muscle weakness. This adverse event was first observed in tipifarnib-GBR-1.(Howes et al, 2003) In the first cohort, 15 of 41 participants (37%) treated continuously developed neurotoxicity, of which several were severe and long lasting. In contrast, 1 of 35 participants (2.9%) in the second cohort treated cyclically experienced neurotoxicity. In the large Phase 3 colorectal cancer study(Palmer, Thibault et al 2003), neuropathy was reported by 16.3% of participants treated with tipifarnib (1.7% were Grade 3 or 4) and 12% of participants receiving placebo (all Grade 1 or 2).

Other AEs reported on tipifarnib trials but with an unknown relationship to tipifarnib were tachycardia, palpitation, hypotension, peripheral edema, fever, rigors, weight decrease, erythematous rash, alopecia, hot flashes, dehydration, dyspepsia, constipation, flatulence, stomatitis, pharyngitis, taste perversion, dry mouth, intestinal obstruction, ileus, hyperbilirubinemia, increased SGOT (aspartate aminotransferase), sepsis, muscle weakness, hypomagnesemia, hyperglycemia, hypercalcemia, increased lactic dehydrogenase, elevated amylase, elevated lipase, paresthesia, dizziness, tremor, extrapyramidal reaction, involuntary movements, dysphonia, depression, seizures (2 cases), abnormal vision, chest pain, arthralgia, myalgia, headache, abdominal pain, pneumonia, pneumonitis, pulmonary infiltrates, dyspnea, cough, hiccoughs, increased creatinine, dysuria, urinary tract infections. Because of preclinical toxicity studies (see above), initial human trials of tipifarnib included extensive ophthalmologic evaluation for development of cataracts. None were observed.

Most of the deaths occurred at doses above 300 mg bid and were in subjects with leukemia. The majority of fatal adverse events (58/88, 66%) were related to infection (sepsis, pneumonia, infection, infection fungal and infection bacterial). Hemorrhage (intracranial, pulmonary, GI or vascular hemorrhage) accounted for 15/88 fatal events (17%).

Myelosuppression (granulocytopenia, leucopenia, pancytopenia, anemia and thrombocytopenia) accounted for 12/88 fatal events (14%).

2.7 Conclusion

Tipifarnib as single agent appeared to have promising activity in AML in early phase clinical trials. Tipifarnib was granted “Fast Track” status by the FDA in 2004 and was also granted Orphan Drug status. However, in 2005 FDA did not grant approval for tipifarnib, a request based on Phase II data. Subsequently, a Phase III study did not confirm activity as a single agent for the treatment of older AML patients.

Other uses of tipifarnib are being investigated in trials supported by CTEP, including the two phase I trials discussed previously investigating the addition of tipifarnib to induction AML therapy (Karp, Hatten et al 2009; Brandwein et al, 2009). There is also interest in examining the potential benefit of tipifarnib maintenance therapy in poor-risk AML. In a phase II trial, maintenance tipifarnib at a dose of 400 mg bid for 14 or 21 doses was given for a maximum of 16 cycles (48 weeks) in poor-risk AML patients achieving first remission (Karp, Smith, et al, 2008). Compared to historically similar patients, the authors observed disease free prolongation in patients with secondary AML and adverse cytogenetics. These results suggested that tipifarnib maintenance might be beneficial for subsets of patients with poor-risk AML. Based on these results, ECOG 2902 is conducting a phase III trial of maintenance tipifarnib versus observation alone in poor-risk AML patients in remission. This study has met its accrual goal of 139 patients. Follow-up and data analyses are ongoing and results of this study are eagerly awaited.

2.8 Expert Opinion

The future of tipifarnib is uncertain at this time. It is the authors' understanding that Johnson & Johnson Pharmaceutical is no longer supporting tipifarnib as a therapeutic for AML because of the negative Phase III trial utilizing tipifarnib as a single agent. Therefore, further development of tipifarnib for MDS/ALM therapeutics appears questionable. However, utilization of tipifarnib in other settings such as maintenance therapy or in combination with induction therapy may prove to be useful. Combinations of FTI and inhibitors of cholesterol synthesis simvastatin have apoptosis promoting effects in combination against human CD34+ AML cell lines *in vitro* (van der Weide, et al., 2009). Although not yet tested in the clinical setting, these results suggest that the combination of tipifarnib and statins may be better than single agent in some AML patients. The future of tipifarnib lies in achieving a better understanding of the mechanism of clinical response and the use of predictive biomarkers for patient selection. The predictive power of the ratio of *RASGRP1/APTX* gene expression not only provides a potentially important biomarker of response, it also suggests that responsive patients have underlying pathology related to abnormalities in the DNA excision repair pathway (Raponi, Lancet et al. 2008). Validation of this predictive marker is critical for future therapeutic approaches and may generate important information that will restore interest in tipifarnib as an active agent in AML and MDS.

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2.9 Drug summary box

Drug summary box

Drug name	tipifarnib
Phase	Phase 1, 11 and 111
Indication	Acute Myeloid Leukemia (investigational)
Pharmacology description/ mechanism of action	methyl-quinolinone derivative that acts as a potent and selective nonpeptidomimetic inhibitor of farnesyl tranferase protein (FTP)
Route of administration	oral
Chemical structure	molecular formula C ₂₇ H ₂₂ Cl ₂ N ₄ O
Pivotal trials	See table 2

Figure 1. Summary of Ras signaling pathway

RAS is activated by receptor tyrosine kinase (RTK) activation with several ligands that invoke these intermediates. Activation of the receptor leads to the activation of Ras nucleotide exchange factors such as GRB-2 and SOS that mediate the exchange of GDP for GTP and the recruitment of Raf and the activation of downstream factors such as Rac, Rho that mediate changes in the cytoskeleton, MEK and MAPK that mediate proliferation and PI3K and AKT that are necessary for survival. Other factors that mediate transcription such as the Janus Activating Kinase (Jak) lead to the Signal Transducer and Activator of Transcription (STAT) phosphorylation and transcription. This pathway has also been linked to tipifarnib response but the mechanism is unknown.

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Table 1

Known farnesylated proteins that may be molecular targets for tipifarnib.

Protein Target*	Prenylation Sequence	Function
H-Ras	CSVL	GTPase
Rheb	CSVM	GTPase
Rheb2	CHLM	GTPase
HDJ2	CQTS	Unknown
K-Ras	CVIM	GTPase
N-Ras	CVVM	GTPase
CENP E	CKTQ	Kinesin motor protein
CENP E	CKVQ	Chromosome passenger protein
Prelamin A	CSIM	Nuclear envelope
Rho B	CKVL	GTPase
PRL1,2,3	CCIQ, CCVQ, CCVM	Tyrosine phosphatase
Rho D	CCVT	GTPase
Rho 6	CSIM	GTPase
Rho 7	CNLM	GTPase
Tc10	CLIT	GTPase

* Adaptation from Basso, AD et al. J Lipid Res 2006; 47:15-31.²⁴

Table 2

Therapy of AML with single agent tipifarnib.

	Author	Response	Dose-Schedule	Patients
Phase I				
	Karp, Lancet (2001)	2/34 (8%) CR	100–1200, 21 of 28 days	relapse/refractory
	Kirschbaum (2007)	3/9 (33%) CR	400–1400, alternate week	relapse/refractory
	Karp, Flatten (2009)	Response based on dose (N=84)	Combination therapy tipifarnib and etoposide	Newly diagnosed Age > 70
	Brandwein (2009)	10/22 (45%) CR	Combination therapy with conventional induction and consolidation therapy	Newly diagnosed Age > 70
Phase II				
	Karp, Smith (2008)	15/48 (31%), continuous CR for median 28+ months	400 mg bid 14 of 21 days 48 weeks	poor-risk AML
	Harousseau (2007)	11/169 (7%) months	600, 21 of 28 days	relapse/refractory
	Lancet (2007)	22/158 (14%) months	600, 21 of 28 for 63 days	Poor risk age ≥ 65
Phase III				
	Harousseau (2009)	18/228 (8%) compared to hydroxyurea	600, 21 of 28 days	Newly diagnosed, Age ≥ 70