J-L. Harousseau

Centre Hospitalier
Universitaire Hôtel-Dieu
Place Alexis Ricordeau
Nantes, France

Tipifarnib in hematologic malignancies

Farnesyltranferase inhibitors (FTI) are signal transduction inhibitors that block farnesylation of a number of proteins including Ras that are involved in key cellular functions (proliferation,survival and differentiation).[1,2] Tipifarnib is a potent inhibitor of farnesyltransferase that is orally bioavailable. Tipifarnib was initially developed with the goal of targeting Ras in cancers with a high incidence of Ras mutations. However, after failure of large clinical trials in solid tumors (pancreas,colon) further development was mainly focused on hematologic malignancies

Tipifarnib in AML

The rationale for evaluating tipifarnib in AML was that AML cells constitutively express effectors or activate pathways that are involved in cell proliferation and survival and that are targeted by FTI, mostly Ras which is frequently deregulated in AML.[1,2]

Phase I study

In a Phase I dose-escalation study, Tipifarnib was administered twice daily (bid) for 21 consecutive days to 34 adult patients with poor-risk AML.[3] Doses ranged from 100 mg to 1200 mg and dose-limiting toxicity (central nervous system) occurred at the 1200 mg level.Non dose-limiting toxicities were fatigue, nausea, renal dysfunction. Myelosuppression was observed mostly at the 600 mg and 900 mg levels. Clinical responses were seen in 10 patients with 2 complete remissions (CR). Interestingly responses were not related to the Ras mutations status

Phase II studies

Based on these encouraging results, two Phase II studies were initiated with tipifarnib at a dose of 600 mg bid for 21 consecutive days.

First, a large international study enrolled 252 patients with either refractory (117 patients) or relapsed (135 patients) AML.[4] The median age was 62 years. Overall, the drug was well tolerated, with myelosuppression as the major toxicity. Nonhematologic toxicity was mild and the incidence of grade 3 or 4 adverse events was 25%. Only 11 patients achieved CR, 4% of the intent-to-treat population and 7% of the 169 patients who received at least one cycle of treatment. Patients achieving CR had a median overall survival (OS) of 1 year. Moreover, bone marrow blasts were reduced by 50% in 27 patients (11%). Although this study confirmed that tipifarnib

has some antileukemic activity, the results were rather disappointing and two questions were then raised

Is 600 mg bid the optimal dose?

Results from a dose-ranging pharmacodynamic study that measured HDJ2 prenylation before and after tipifarnib treatment in 23 patients with hematologic malignancies showed that the highest level of farnesylation occurred at the 300 mg bid level[5]

Explorations of other doses and schedules are underway. In a Phase II 4-arm study, two doses (300 mg and 600 mg bid) and two schedules (daily for 21 days or one week on, one week off) were administered to patients with newly diagnosed AML, over age 70 and unfit for conventional chemotherapy.[6] Best results were obtained in patients who received tipifarnib 300 mg bid for 21 days

Is it possible to predict which patients will respond to tipifarnib?

A pharmacogenomic analysis was performed in parallel with the clinical study and gene expression profiles from 80 bone marrow samples were analyzed.[7] Supervised statistical analysis identified a set of 8 genes that might predict response to tipifarnib. The most robust was AKAP 13 which was overexpressed in patients resistant to tipifarnib

Secondly, a Phase II study was conducted in 158 elderly patients with previously untreated poor-risk AML.[8] The median age was 74, 75% of patients had antecedent MDS, 47 % had adverse cytogenetics. Treatment-related mortality was 7%. The CR rate was 14% .Of note 40% of CR patients had adverse cytogenetics. Median duration of CR was 7.3 months and median OS for CR patients was 18.3 months. Again there was no correlation between response and Ras mutations status.

Phase III study

A randomized Phase III study (Table 1) comparing tipifarnib 600 mg bid for 21 days versus best supportive care (including hydroxyurea if needed) in 457 patients over the age of 70 with newly diagnosed poor-risk AML who were unfit for conventional chemotherapy.[9] The median age was 76 years and I/3 patients had unfavourable cytogenetics. Although durable CR (median DFS 8 months, median OS 22 months in CR patients) was achieved in 18 patients (8%) versus 0 in the control arm, there was no significant benefit in OS with tipifarnib (median 107 days versus 109 days)

Table 1. Phase III randomized trial of tipifarnib versus best supportive care in the treatment of newly diagnosed acute myeloid leukaemia in patients 70 years and older.

	Tipifarnib 600 mg bid 21/28 days N=228	*Best supportive care N=229*
Median age	76	76
> 80 years	22%	26%
ECOG 2	28%	28%
Unfavorable cytogenetics	30%	33%
AML with myélodysplasie	40%	38%
CR	8%	0
PR/Hematologic improvement	9%	1%
Median CR duration	240 days	-
Median Overall survival	107 days	109 days

Tipifarnib in combination

Preclinical studies have shown that the antiproliferative effects in human AML cells are additive when tipifarnib is combined with cladribine or fludarabine and synergistic when it is combined with bortezomib or daunorubicin.[10-12]

The combination of tipifarnib with anthracycline plus ara-C has been evaluated in pilot studies in patients with newly diagnosed AML. The MD Anderson group has obtained 73% CR in 95 patients aged 15-70 without major increase of toxicity compared to the same regimen without tipifarnib.[13] Another Phase I dose-escalation study in elderly patients showed that the addition of tipifarnib is well

tolerated up to 600 mg bid on days 6-15 of induction and consolidation treatment.[14]

Tipifarnib has also been combined with oral etoposide in 84 elderly patients (median age 77 years) unfit for conventional chemotherapy.[15] With a 21-day schedule a high incidence of Grade 3-4 adverse events was observed at tipifarnib doses of 400 mg bid (especially mucositis),independent of etoposide dose. A 14-day schedule was much better tolerated even with tipifarnib doses of 600 mgbid. The CR rate appeared superior with the 14-day schedule (30% *vs.* 17% with a 21-day schedule).

Tipifarnib in maintenance therapy

Tipifarnib monotherapy has also been investigated as post-consolidation maintenance therapy in adult AML patients.[16] In a multicenter, open-label Phase II trial, tipifarnib was administered at a dose of 400 mg bid for 14 out of 21 days in 48 patients with poor-risk AML in first CR, after recovery from consolidation chemotherapy, for a maximum of 16 cycles. Twenty (42%) received 16 cycles. Tipifarnib dose was reduced in 58% of cases for myelosuppression but non hematologic toxicities were rare. An historical comparison with similar patients not reciving tipifarnib suggested a benefit of maintenance with tipifarnib in patients with poor-risk features (adverse cytogenetics and/or antecedent MDS).

Current questions

Although tipifarnib clearly has an antileukemic activity, the CR rate achieved in monotherapy remains low both in relapsed/refractory AML and in elderly patients unfit for conventional chemotherapy. The future of the drug is more likely in combination. However the key question is to understand which patients may respond to tipifarnib. Gene expression profiling studies may be hepful is this context. In addition to studies performed in relapsed/refractory patients Raponi et al have conducted a study in parallel to the Phase II clinical trial performed in newly diagnosed elderly patients.[17] They have found that response to tipifarnib relates to the expression of two genes: upregulation of the guanine nucleotide exchange factor RASGRP1 which activates Ras,and downregulation of APTX, the gene that encodes excision repair protein aprataxin.

The precise mechanism by which tipifarnib exerts its antileukemic activity remains to be defined. Since there is no correlation between CR achievement and Ras mutations, the idea that FTI are active by targeting Ras mutations is at least incomplete. It is likely that FTI have an impact on multiple molecules and several pathways involved in cellular survival and proliferation, including the PI3/AKT pathway. A better knowledge of the mode of action of these agents would certainly help to define subgroups of patients that might respond and/or optimal combinations

Tipifarnib in myelodysplastic syndromes

Like in AML, the rationale for testing tipifarnib and FTI in MDS was initially the incidence of activating mutations of Ras in these diseases. But again, responses were unrelated to the mutational status and other mechanisms of action are proposed.

A single-center Phase I dose-escalation study included 21 patients (median age 66 years).[18] The initial dose was 300 mg bid for 21 consecutive days, and the dose was escalated by 100 mg/day in 3-patient cohort until grade 3 toxicities were noted. Dose-limiting toxicity (fatigue) was observed at the 450 mg bid level. Objective responses were seen in 6 of 20 evaluable patients (including 1 CR).

This trial was followed by a Phase II single-center study in 27 patients (median age 66

years) with tipifarnib at the dose used in AML (600 mg bid).[19] This higher dose resulted in numerous toxicities including myelosuppression, fatigue, neurotoxicity, rash,that necessitated dose reduction or discontinuation of treatment in 41% of patients. Responses were seen in only 3 cases (2CRs)

In a multicenter international Phase II trial, 82 intermediate and high-risk MDS patients were treated with 300 mg bid for 21 consecutive days.[20] Median age was 67 years, 40% of patients had RAEB with >10% blasts and 23% had RAEB in transformation. The overall reponse rate was 32% with 12 (15%) CR. The median CR duration was 11.5 months. Median OS was 11.7 months. Grade 3 neutropenia (18%) and thrombocytopenia (32%) was the most common treatment-related adverse event. Severe nonhematologic toxicities were rare. CR were seen in all WHO classes without correlation to the IPSS score. Three patients with cytogenetic abnormalities has complete cytogenetic responses.

Another study evaluated a one week-on/one week-off schedule.[21] This dose-escalation study enrolled 63 patients (median age 68 years). Again the most common toxicity was myelosuppression (60% of patients). Nonhematologic toxicities included fatigue (20%), skin rash (9%), diarrhea (16%), increase in liver transaminases (14%) and bilirubinemia (11%). Dose-limiting toxicities occurred at doses above 1200 mg/day. The response rate was 26% with 3 CR. There was no obvious dose-response relationship and only one responder had a Ras mutation

Although these results are encouraging, the place of FTI in the treatment of MDS remains to be defined, particularly since the introduction of demethylating agents (azacytidine and decitabine) is changing the scene.[22] These agents are becoming standard therapy in higher risk MDS to which newer agents should be either compared or combined.

Tipifarnib in chronic myeloid leukemia

Imatinib is the standard of care in CML, and induces complete hematologic responses and major cytogenetic responses in 95% and 85 % respectively. However imatinib fails to eradicate quiescent Bcr-Abl positive stem-cells and a subset of patients develop imatinib-resistance.[23] One strategy to overcome imatinib-resistance is to interfere with Bcr-Abl downstream pathways such as the Ras pathway. Preclinical studies have suggested that FTI can inhibit proliferation or induce apoptosis in imatinib-resistant cell lines or cells from patients.[24-26]

In a clinical study on 22 patients with CML (77% resistant to imatinib),tipifarnib showed a modest activity with 7 complete or partial hematologic responses and 4 minor cytogenetic responses.[27]

In vitro FTI have proven synergistic with imatinib both in imatinib-sensitive and imatinib – resistant cell lines.[28] Based on these results, the combination of imatinib and tipifarnib has been evaluated in patients with CML after imatinib failure. In a Phase I study on 26 patients, the initial dose level was tipifarnib was 300 mg bid and imatinib 300 mg/day.[23] Therapy was escalated following a 3+3 design and the maximum tolerated dose was tipifarnb 400 mg bid and imatinib 400 mg /day. Adverse events included diarrhea (81%) and nausea (69%) but wre usually grade 2 or less; Grade 3-4 neutropenia and thrombocytopenia occurred in 42% nad 31% of patients respectively. Hematologic responses were obtained in 68% of evaluable patients and 36% achieved a cytogenetic response (including 3 complete responses and 4 partial responses). One patient with the highly resistant T351I mutation achieved a partial cytogenetic response. Therefore this combination is well tolerated and active in patients with imatinib-resistant CML. Although new tyrosine-kinase

inhibitors (dasatinib, nilotinib) are currently indicated in this indication, the potential advantage of FTI is their activity against quiescent leukemic stem cells which are insensitive to available tyrosine-kinas inhibitors and can facilitate resistance to imatinib.

Conclusions

Tipifarnib is an oral agent that is well tolerated and has some activity in AML,MDS and CML. However its efficacy is relatively modest when given as a single agent. In a large Phase III randomized trial in elderly patients with AML unfit for chemotherapy, tipifarnib has not proven significantly superior to best supportive care in terms of OS. Therefore, for the future combinations appear more attractive. Another hope is a better definition of the mode of action and of factors predicting response.

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