Response:

Chromosomal abnormalities in Ph-negative cells

Several case reports and small studies have appeared that describe clonal cytogenetic abnormalities in Ph-negative cells of chronic myeloid leukemia (CML) patients treated with imatinib. Trisomy 8 and monosomy 7 are most frequent, but other aberrations have also been reported.1

The cases published thus far were in late chronic or accelerated phase. Thus, the patient described by McMullin et al is unusual, since he had received only a short course of hydrea prior to imatinib. To our knowledge, there is only one similar published case. This patient exhibited t(2;11) both in Ph-negative and Ph-positive cells, implying that this aberration was present before the Philadelphia translocation was acquired,2 in contrast to the case of McMullin et al, where the abnormalities were confined to Ph-negative cells.

One of the main issues raised by these observations is whether imatinib has a direct mutagenic effect. Preclinical studies showed that imatinib and some of its intermediates are genotoxic in vitro.3 In vivo effects of intermediates can be excluded, since they are not present at relevant concentrations in the purified drug. Clastogenic effects of imatinib occurred in only one in vitro chromosome aberration assay at the highest concentration (125 mg/L), which is highly cytotoxic and exceeds drug levels achieved in patients by several orders of magnitude.4 Effects such as this are not unusual and known as high-toxicity clastogenicity (J. Ford and D. Roman, personal written communication, July 2003). In addition, in our study,5 we observed an association between chromosomal abnormalities in Ph-negative cells and prior exposure to cytarabine and idarubicin, arguing against a direct genotoxic effect of imatinib. Moreover, if imatinib was directly genotoxic, one would expect a similar incidence in newly diagnosed patients after comparable follow-up. The median time on imatinib in the patients with abnormalities in our study was 16 months.5 This is shorter than the 19 months median follow-up in the randomized comparison of imatinib versus interferon-alpha/cytarabine in newly diagnosed patients.6 Since abnormalities in Ph-negative cells were not specifically captured in this study, underreporting cannot be excluded. However, an incidence of 15% as in our study would hardly have gone undetected.

Thus, it seems likely that the proliferative stress placed on a small number of Ph-negative stem cells to restore hematopoiesis in the presence of imatinib may be more important. In this case, patients whose disease has evolved over a longer period of time before diagnosis will be at higher risk, due to their smaller pool of Ph-negative progenitor cells. The patient described by McMullin et al did not achieve a major cytogenetic response until 12 months, unlike most newly diagnosed patients.6 This may indicate that his disease, though in chronic phase by definition, was in fact in a later stage of evolution. Damage to Ph-negative stem cells by previous exposure to cytotoxic agents would add to the risk, consistent with our findings.5 Whether the stress to Ph-negative cells is aggravated by inhibition of Kit remains speculative; Kit mutant mice exhibit compromised hematopoiesis but are not prone to leukemia.7

In reality, the 2 possibilities cannot be distinguished with certainty. What might be more revealing is whether similar abnormalities appear in solid tumor patients treated with imatinib. No less important than the etiology of this phenomenon is its prognosis. Progression to myelodysplastic syndrome (MDS) has occurred in several patients, and a decision to proceed to allografting was made.8 Given the dismal prognosis of chromosome 7 abnormalities in MDS, this is certainly justified. However, the significance of other abnormalities, particularly isolated trisomy 8 in the absence of dysplastic changes, is less clear. For adequate counseling of patients, a systematic collection of information is required. A registry has been set up at Oregon Health & Science University, to which contributions are invited.

References

2. Royer-Pokora B, Hildebrandt B, Redmann A, et al. Simultaneous occurrence of a t(9;22) (Ph) with a t(2;11) in a patient with CML and emergence of a new clone with the t(2;11) alone after imatinib mesylate treatment. Leukemia. 2003;17:807-810.

To the editor:

Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses

Imatinib at the standard dose of 400 mg daily induces complete cytogenetic remissions (CCyRs) in 40% of patients with chronic myeloid leukemia (CML) in chronic phase who had previously failed interferon-alpha (IFN-alpha),1 and in 75% of newly diagnosed patients.2 However, the optimal treatment for patients who do not achieve or who lose a CCyR is uncertain. It is theoretically possible that such patients could benefit from higher doses of imatinib. Kantarjian et al3 recently reported that 19 (56%) of 34 patients

Correspondence: Michael W. N. Deininger, BMT/Leukemia Center, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail code L592, Portland, OR 97239; e-mail: deininger@ohsu.edu.

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classified as cytogenetically resistant on imatinib at 400 mg daily subsequently improved cytogenetically when the imatinib was increased to 600 or 800 mg daily; they therefore advocated this strategy for patients with primary or acquired resistance to imatinib. We report here results of increasing imatinib dosage in patients who failed to obtain CCyR on 400 mg/d.

We studied 36 consecutive patients with CML in chronic phase in complete hematologic response whose imatinib dosage was increased when they failed to achieve a CCyR on an initial dose of 400 mg daily; 9 (25%) were newly diagnosed and 27 (75%) were IFN-α failures. The median time from starting imatinib to dose increase was 383 days (range, 366-1083 days) and the median time on the increased dose (to latest follow-up) was 416 days (range, 212-790 days). At the time of dose increase, 18 patients were 100% Philadelphia positive and the 18 had varying degrees of Philadelphia negativity. Of the 36 patients, 23 (64%) were then treated with imatinib at 600 mg/d, 12 (33%) received 800 mg/d, and 1 (3%) received 1000 mg/d.

We judged the increased dose to have been effective if there was a change from partial cytogenetic response (PCyR) to CCyR, or from minor cytogenetic response (MiCyR) to PCyR or CCyR, or from no cytogenetic response to MiCyR, PCyR, or CCyR. Fourteen patients (39%) improved their cytogenetic responses and 7 (19%) achieved CCyR. Unfortunately, many of these responses were short lasting, and at latest follow-up 6 (43%) had lost their best response. At latest follow-up only 9 (25%) still had sustained improvement including 5 (14%) patients who remained in CCyR.

In multivariate analysis the only factor that predicted improved cytogenetics was the level of Philadelphia positivity when the higher dose was started. Of 18 patients who were 100% Philadelphia positive at that time only 1 (6%) had a sustained cytogenetic improvement and none achieved CCyR; conversely, of the 18 patients who had some degree of Philadelphia negativity, 8 (44%) had a sustained response and 5 (28%) achieved CCyR (P = .018 and P = .045, respectively).

We do not believe that our data support the notion that increasing the dose of imatinib can durably overcome primary or acquired resistance, particularly in patients who fail to obtain any degree of Philadelphia negativity on 400 mg daily. Our experience and that of Zonder et al contrast with that of Kantarjian et al. We conclude that there is little to be gained by increasing the imatinib dose for such patients; rather, one should consider adding other agents to the imatinib or possibly allogeneic stem cell transplantation.

David Marin, John M. Goldman, Eduardo Olavarria, and Jane F. Apperley

Correspondence: John M. Goldman, Department of Haematology, Imperial College School of Medicine at Hammersmith Hospital, Ducane Road, W12 ONN London, United Kingdom; e-mail: j.goldman@ic.ac.uk

References

Response:

Dose escalation of imatinib may improve responses in patients with CML who fail standard-dose imatinib

We are gratified to note that Marin et al have confirmed our study regarding the clinical benefit of increasing the dose of imatinib in patients with Philadelphia chromosome (Ph)–positive chronic myelogenous leukemia (CML) not in complete cytogenetic remission (CCyR). In our report, 13 (38%) of 34 patients treated achieved a major cytogenetic response (MCR). Zonder et al reported an MCR in 6 (38%) of 16 patients (2 additional patients with clonal evolution lost the additional clone, remaining 100% Ph-positive). These results are similar to those of Marin et al: 14 (39%) of 36 patients improved their cytogenetic response upon increasing the dose. The issue at question is the durability of these responses. Marin et al reported that 43% of patients have lost their response, while 9 (25%) had sustained improvement (5 [14%] with CCyR). Zonder et al reported 3 of 6 responding patients maintaining their response for 18+ months. We reviewed the status of the patients that had responded in our study. With a median follow-up of 18 months, 8 (62%) of 13 patients who achieved an MCR still have an MCR (3 have a CCyR). Among 6 patients that had achieved a CCyR, 2 have now a partial response, and 1 who had a partial response has now achieved a CCyR. The median duration of the improved response is 11 months (range, 1 to 24+ months). In addition, 4 nonresponding patients in our initial report have now achieved a cytogenetic response (3 partial, 1 minor).

Thus, the 3 series support our conclusion that “higher dose imatinib mesylate may overcome disease-poor response to conventional doses.” To that, Zonder et al reached a similar conclusion: “consideration of increasing the dose to 800 mg/d for inadequate cytogenetic response after this amount of time (6 months) seems reasonable.” The notion of adding other agents to imatinib is interesting. We and other investigators are pursuing this approach for imatinib-resistant CML. Patients would benefit from clinical trials investigating these combinations, but to date, there is no data to suggest that any combination is superior to what is obtained with increasing the dose of imatinib. In addition, most of these options are investigational, and many patients are unfortunately not offered participation in clinical trials. The possibility of stem cell transplantation is obviously attractive, but a majority of patients are not candidates for, or refuse, transplantation. That was the case for patients in our series. Therefore, we believe the 3 series support our conclusion that these data encourage the investigation of high-dose imatinib mesylate as frontline therapy in patients with newly diagnosed CML, or in late chronic-phase CML, to obtain better and more durable complete cytogenetic and, possibly, molecular remissions.

Zonder et al reached a similar conclusion: “These results also suggest that future trials explore the role of initial treatment with higher doses of imatinib mesylate to determine whether the cytogenetic CR rate can be improved.” Our early observations with high-dose imatinib suggest this approach may be valuable.

Jorge Cortes and Hagop Kantarjian

Correspondence: Jorge Cortes, Leukemia Department, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 428, Houston, TX 77030; e-mail: j.cortes@mdanderson.org
Congenital dyserythropoietic anemia type II in human patients is not due to mutations in the erythroid anion exchanger 1

Type II congenital dyserythropoietic anemia (CDA-II or HEMPAS) is an autosomal recessive disorder, representing the most frequent form of congenital dyserythropoiesis.

Recently, the molecular basis of the retsina (ret) phenotype that resulted in zebrafish from mutations in the gene that encodes the erythroid anion exchanger 1 (AE1, also called SLC4A1) was reported. The high number of binucleated erythroblasts, the presence of “double membranes,” and the reduction in posttranslational glycosylation of AE1, observed in the ret fish, are all reminiscent of the human CDA-II. Since the gene responsible for CDA-II in humans has not yet been identified, it is highly relevant to ask whether it could be AE1.

In first approximation, this does not seem likely for several reasons. First, as the authors themselves note, in a majority of families with CDA-II that have been subjected to linkage analysis, the disease maps to 20q11.2, whereas AE1 maps to 17q21-q22. Second, complete inactivation of AE1, through its protein 4.1R-binding domain, was found to underglycosylation of AE1 that is characteristic of this condition, and 6, 7, 8, and 9, severe CDA-II. In order to test whether AE1 mutations might be responsible for a subset of patients with CDA-II we have used the resources of an international registry in which 108 patients are enrolled. In 14 of these patients, belonging to 7 unrelated families, the disease was not linked to 20q11.2 (Figure 1A). Of these 14 patients, 6 had a particularly severe form of CDA-II (they were transfusion dependent from the age of 1 year); the remaining 8 patients had “typical” CDA-II. In 5 families we were able to exclude linkage to chromosome 17. In addition, we proceeded in all 14 patients to quantitate erythrocyte AE1 by means of sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). Whereas in patients with HS the amount of AE1 was significantly reduced (73.90 ± 2.42% of controls, P < .0001), in patients with CDA-II the amount of AE1 was virtually normal (96.50 ± 2.07% of controls, P = .783). In terms of the possible pathophysiologic significance of AE1 in CDA-II, while all these patients had the underglycosylation of AE1 that is characteristic of this condition, we did not find any difference in AE1 expression between patients with severe CDA-II versus “typical” CDA-II (96.83 ± 2.48% versus 96.25 ± 1.83%, respectively; P = .621) (Figure 1B).

Based on genetic analysis and on biochemical findings, we suggest that in at least the vast majority of cases human CDA-II is not due to AE1 mutations. It is intriguing that, in zebrafish, AE1, through its protein 4.1R-binding domain, was found to affect the poles of the mitotic spindle specifically in erythroid cells; as a result, AE1 deficiency ultimately affects the completion of chromosome segregation in these cells, thus mimicking certain morphologic features of CDA-II. Therefore, in the rare patients in whom linkage to AE1 has not been ruled out, it will be important to look specifically for mutations within this particular domain of human AE1.