Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate

The tyrosine kinase inhibitor imatinib mesylate (STI-571, Gleevec®) has led to a paradigm shift in our approach to the treatment of chronic myeloid leukemia (CML). Clinical studies carried out in all disease phases have revealed excellent hematological and cytogenetic responses, and hence it has recently been approved as the first-line treatment in CML patients who are not the ideal candidates for allogenic bone marrow transplantation [1]. All recent studies have shown that imatinib is well tolerated. Although most patients experience side effects, these are generally mild (grade I/II). The common non-hematological side effects include nausea, superficial edema, muscle cramps, musculoskeletal pain and skin rashes [1]. Of these, the cutaneous reactions are the most common side effects, which primarily include superficial edema, and skin rash and related events seen in 50% and 34% of patients, respectively [1]. The exact pathophysiology of the cutaneous reactions is unclear. The high prevalence of these adverse events and their relationship with dose suggests that these reactions are probably due to the direct pharmacological effect of imatinib [2].

We enrolled and followed 118 patients with CML between January 2001 and June 2003 in chronic phase (n = 79; 400 mg/day), accelerated phase (n = 22; 600 mg/day) and blast crisis (n = 17; 600 mg/day). At a median follow up of 6 months in this study group, commonly reported cutaneous adverse effects, i.e. superficial edema and rash, were seen in 48% and 12.7% of patients, respectively. A striking event was the high prevalence of pigmentary disturbances in these patients, which included depigmentation (localized or generalized) in 40.9% of cases and of pigmentary disturbances in these patients that included skeletal pain and skin rashes [1]. Of these, the cutaneous reactions are probably due to the direct pharmacological effect of imatinib [2].

In the literature there are few data on pigmentary changes during imatinib therapy. There are a few reports of depigmentation (localized or diffuse) of skin [2], but hyperpigmentation of skin has not been reported so far. A recent report described repigmentation of hair in nine of 133 patients taking imatinib [3]. The frequency of pigmentary changes is much higher in our population. A common factor in our report and the previous reports is the occurrence of these events only in ethnically pigmented patients; this probably explains the difference in reported frequency of pigmentary changes, as our study population was ethnically pigmented.

The molecular basis of these cutaneous changes is unknown at present. Imatinib targets the ATP binding site of BCR-ABL tyrosine kinase, as well as the tyrosine kinases of platelet-derived growth factor receptor-β, C-kit and ABL. C-kit is normally expressed in skin basal cells, melanocytes, epithelial cells of the breast, tissue mast cells and other cells [4]. There are recent data suggesting that C-kit and its ligand stem-cell factor have a major role in melanogenesis, melanocyte homeostasis and UVB-induced pigmentation [5]. The stimulation of C-kit leads to activation followed by rapid degradation of microphthalmia transcription factor (Mi), which transactivates the tyrosinase pigmentation gene promoter in melanocytes [6]. Hence the pigmentary changes, skin rash and related events are likely to be due to imatinib-induced C-kit inhibition in skin. In a recent series of 54 patients, all seven patients who developed hypopigmentation of the skin also had associated skin rash in the area of hypopigmentation, suggesting a common etiology [2]; however, in our series only six (5.4%) patients had associated skin rash, indicating that complex molecular events may be involved.

Imatinib is presently the paradigm of a new class of oral molecular-targeted drugs. Inhibition of multiple tyrosine kinases with varied, but as yet unknown, functional consequences stresses the fact that a clear understanding of these events will definitely be useful in the future treatment of patients.

B. Arora, L. Kumar*, A. Sharma, J. Wadhwa & V. Kochupillai
India Institute of Medical Sciences, 236, RDHMM, 110049 New Delhi, India
(*E-mail: lalitaaiims@yahoo.com)

References

First-line hepatic infusion of pirarubicin in patients with isolated liver metastases: is it really promising?

In a recent issue of Annals of Oncology, Zelek et al. reported on a combination treatment of systemic [5-fluorouracil (5-FU), leucovorin (LV) and irinotecan] and hepatic arterial (pirarubicin) chemotherapy in the first-line treatment of non-resectable, metastatic colorectal cancer limited to the liver [1]. In their article, the authors report a response rate of 48% and a median survival of 20.5 months. Thirty-one patients were enrolled on the study and liver resection was possible in 11 responding patients. The median survival of resected patients was not reached, while the unresected group had a dismal median survival of 13.9 months. The authors conclude that regimens combining systemic and hepatic infusion chemotherapy deserve further investigation.

Reviewing this study, I find the results obtained very disappointing. By limiting patient enrollment to patients with hepatic metastases only, one would expect that the study outcome would be more favorable than what had been described with systemic chemotherapy alone. Instead, as the authors point out, responses were similar to what has been described with FOLFOX or FOLFIRI combinations [2–4]. Furthermore, the outcome of patients with unresected disease was disturbingly poor compared to newer combinations. Attributing these findings to a poor prognosis patient population is certainly not justified given the strict eligibility criteria.

Of further concern is the lack of a favorable disease control rate with this combination. This is exemplified by a stable plus partial response rate of 71%, which does not compare favorably with a rate exceeding 80% with systemic combinations of 5-FU/LV and oxaliplatin or irinotecan. This could be secondary to the inability to administer full doses of effective systemic chemotherapy. The study does not even suggest a better hepatic disease control as evidenced by first-site disease progression in the liver in >80% of the initial responders. As far as the high resectability rate in this highly selected population, it can certainly be attributed to patient selection rather than the addition of hepatic arterial infusion.

The authors also point out that this combination therapy compares favorably to other combinations of systemic chemotherapy and hepatic arterial infusion, citing studies by Copur et al. [5] and Kemeny et al. [6]. In my opinion, these are unjustified comparisons as the first study involved a clearly inferior systemic chemotherapy (5-FU/LV) alternating with hepatic infusion, while the other enrolled a majority of pre-treated patients.

Caution should be exercised when developing newer combinations of systemic and hepatic chemotherapy in the front-line therapy of patients with metastatic colorectal cancer. Such combinations may be associated with significant patient inconvenience and increased expenditure to the health care system while a patient benefit continues to be lacking.

M. Fakih*
Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY, USA.
(*marwan.fakih@roswellpark.org)

References

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