

COMMENTED SUMMARIES FROM CURRENT MEDICAL LITERATURE

APPLICATIONS OF MOLECULAR DIAGNOSTICS; SOLID TUMOR GENETICS CAN DETERMINE CLINICAL TREATMENT PROTOCOLS

Summary: Solid tumor diagnosis is now entering an era in which molecular genetics plays an important role. Clinical trials have shown different responses to various therapies that correlate with molecular alterations. Biological determinants, related to treatment-response markers which have aimed at individualized therapies, are being defined and implemented. Patients are now being treated based on the profile of molecular genetic alterations in individual tumors. Protocols based on molecular markers will increase the chances for cure by opting for the right management approach. In most situations, they also will improve the quality of life of patients with cancer, for example by facilitating organ preservation strategies. The molecular characterization therefore, has an important prognostic and practical role in diagnosis.

Comment: The end of the 20th century and the dawn of the 21st century afford an excellent situation to study the position of pathology in the past, present and the future. Application of many ancillary techniques such as DNA manipulation, mRNA production, and proteomics, broke the conventional traditions of morphology and focused on the dramatic changes occurring in pathology as a consequence of molecular and cellular biology findings.

Now that the human genome project is almost complete, academies and companies are shifting their emphasis to the study of how genes vary among people, since the DNA template won't describe every gene outcome. The variations known as single nucleotide polymorphisms (SNPs) are simple chemical substitutions of only one letter of the DNA alphabet, which makes considerable differences between individuals. The idea of proteomics has become the main subject of investigation in different fields of research including therapeutics and pharmacology.

Pharmacogenomics is taking the drug industry by storm. The term coined only four years ago, now encompasses many activities in biotechnology companies and scientific laboratories. This is an era of tradition in medicine from the time of "one size of drugs fits all", in which drugs were manufactured and marketed to all patients, to the time of emerging approach of "personalized medicine", in which drugs are geared to the specific genetic/proteomics makeup of groups or individuals. The study of Cordon-Cardo promises new trends both in diagnosis of solid tumors as well as in the personalized therapeutic management of tumors. In our community there are still problems in using such kinds of applications. Until we could have our own technology, it is not wise to leave the conventional approach to the supposed benefits of these new and sophisticated biotechniques. These must be considered as another diagnostic tool rather than an alternative to the conventional morphology. As discussed by Professor Juan Rosai in the same issue of *Journal of Modern Pathology* (2001; 14: 258-60), the role that morphology plays and will probably continue to play in the molecular age, still validated diagnostic pathology as well as investigations about tumors.

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Source: Cordon-Cardo C. *Mod Pathol.* 2001; 14: 254-7.

EFFICACY AND SAFETY OF A SPECIFIC BCR-ABL TYROSINE KINASE INHIBITOR IN DIFFERENT TYPES OF LEUKEMIA

Summaries: 1) BCR-ABL is a constitutively activated tyrosine kinase that causes chronic myeloid leukemia (CML). Since tyrosine kinase activity is essential to the transforming function of BCR-ABL, an inhibitor of the kinase could be an effective treatment for CML. We conducted a phase 1, dose-escalating trial of STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase. STI571 was administered orally to 83 patients with CML in the chronic phase in whom treatment with interferon alfa had failed. Patients were successively assigned to 1 of 14 doses ranging from 25 to 1000 mg per day. Adverse

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effects of STI571 were minimal; the most common were nausea, myalgia, edema, and diarrhea. A maximal tolerated dose was not identified. Complete hematologic responses were observed in 53 of 54 patients treated with daily doses of 300 mg or more and typically occurred in the first four weeks of therapy. Of the 54 patients treated with doses of 300 mg or more, cytogenetic responses occurred in 29, including 17 (31 percent of the 54 patients who received this dose) with major responses (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome); 7 of these patients had complete cytogenetic remissions. STI571 is well tolerated and has significant antileukemic activity in patients with CML in whom treatment with interferon alfa had failed. Our results provide evidence of the essential role of BCR-ABL tyrosine kinase activity in CML and demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in a human cancer.¹

2) BCR-ABL, a constitutively activated tyrosine kinase, is the product of the Philadelphia (Ph) chromosome. This enzyme is present in virtually all cases of chronic myeloid leukemia (CML) throughout the course of the disease, and in 20 percent of cases of acute lymphoblastic leukemia (ALL). On the basis of the substantial activity of the inhibitor in patients in the chronic phase, we evaluated STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase, in patients who had CML in blast crisis and in patients with Ph-chromosome-positive ALL. In this dose-escalating pilot study, 58 patients were treated with STI571; 38 patients had myeloid blast crisis and 20 had ALL or lymphoid blast crisis. Treatment was given orally at daily doses ranging from 300 to 1000 mg. Responses occurred in 21 of 38 patients (55 percent) with a myeloid-blast-crisis phenotype; 4 of these 21 patients had a complete hematologic response. Of 20 patients with lymphoid blast crisis or ALL, 14 (70 percent) had a response, including 4 who had complete responses. Seven patients with myeloid blast crisis continue to receive treatment and remain in remission from 101 to 349 days after starting the treatment. All but one patient with lymphoid blast crisis or ALL has relapsed. The most frequent adverse effects were nausea, vomiting, edema, thrombocytopenia, and neutropenia. The BCR-ABL tyrosine kinase inhibitor STI571 is well tolerated and has substantial activity in the blast crises of CML and in Ph-chromosome-positive ALL.²

Comment: Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder characterized by leukocytosis and accumulation of all forms of mature and immature granulocytes. The disease is one of the most common types of leukemia in Iran and has a median survival of 3 to 5 years. First described by Nowell and Hungerford in 1960, CML is classically associated with the presence of Philadelphia chromosome that is present in about 95 percent of patients with CML and 20 percent of patients with AML. Philadelphia chromosome results from reciprocal translocation of genetic materials of chromosomes 9 and 22. The resultant fusion product, BCR-ABL, encodes for a fusion protein, which possesses dysregulated tyrosine kinase activity and acts as a mitogen. BCR-ABL also inhibits apoptosis, and thus leads to accumulation of the affected cells. Moreover, BCR-ABL blocks normal integrin function and thus reduces adhesion of progenitor cells to stromal elements so that the stem cells escape physiological inhibitory regulations.

Fowlers was the first to use arsenicals in the treatment of CML in 1856. Later on, radiation therapy was found to be useful in controlling the signs and symptoms of CML and remained the mainstay of treatment until the 1950s. However, soon after radiotherapy was replaced by busulfan and hydroxyurea for their better results and fewer side effects. In the 1980s, interferon was shown to be effective and has now become the first line of therapy for the majority of patients with CML.

Nonetheless, with all of these therapeutic modalities, the disease still has a grave prognosis. The advent of BCR-ABL tyrosine kinase inhibitor, STI571, as was shown in the preceding summaries, marked a revolution in the treatment of CML. Although this expensive drug is still not in the market of many developing countries, its extraordinary therapeutic outcome makes it an acceptable choice for many of the necessary hospital admissions and as an alternative to the other means of therapy used for untreated CML patients. The drug was shown to be effective in both blast crisis and chronic phase of the disease. Considering the long duration of chronic phase that requires long-term treatment with the expensive drug, interferon, provisions should be made by WHO authorities for easier access of developing countries.

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Sources:

1. Druker BJ, Talpaz M, Resta DJ, et al. *N Engl J Med.* 2001; **344**:1031-7.
2. Druker BJ, Sawyers CL, Kantarjian H, et al. *N Engl J Med.* 2001; **344**: 1038-42.