Comparison of the Usefulness and Costs of Bcr-Abl Analysis Versus Chromosome Analysis

Purpose - To determine whether bcr-abl analysis can be utilized to replace cytogenetics in certain hematopoietic malignancies and to evaluate the clinical efficacy and economic impact of such a move in the Tri-hospital community.

Background

CML is associated with Ph1 (the Philadelphia Chromosome). Ph1 is the result of a reciprocal translocation between a portion of the long arm of chromosome 9 and the long arm of chromosome 22. The translocation involves two genes. Specifically, it involves the transposition of the c-abl proto-oncogene on chromosome 9, which codes for a tyrosine protein kinase, to the 5' part of the bcr (breakpoint cluster region) gene on chromosome 22, whose role is unclear (1,2). The end result is that the proximal bcr gene sequences are juxtaposed to the c-abl sequences in a head-to-tail fashion forming a chimeric bcr-abl gene on chromosome 22. The usurpation of the N-terminal of c-abl by the bcr moiety dysregulates the tyrosine kinase activity of the gene, which appears to be responsible for the development of leukemia (3). The translocation of information from c-abl to bcr results in the generation of novel restriction fragments which are diagnostic for the rearrangement of bcr. The precise point of breakage within bcr is unique in most patients with CML but generally occurs between bcr exons 2 and 3 or exons 3 and 4 (1). These rearrangements can be detected by digesting the patient's DNA with a restriction endonuclease and hybridizing the resultant blot with a relevant gene probe. About 98% of patients with CML who have the Ph1 gene have been found to have bcr rearrangements using a standard probe (1).

In the 5-10% of CML patients who do not have Ph1, 50% have classic clinical features and a bcr rearrangement (4,5). These represent complex translocations involving chromosomes 9 and 22 and are identical to Ph1 positive CML patients with regard to clinical course and response to therapy (6). Bcr-abl rearrangements are present in these cases. In published studies, the remainder were
reexamined and could be reclassified as CMML or "atypical CML" based on morphology and/or clinical course(4). "Juvenile CML" is dissimilar to adult CML and is Ph1 negative and rearrangement negative(4).

Acute leukemia may also be associated with Ph1(7). In adults, Ph1 positive ALL may occur de novo or result from lymphoid blast crisis of CML. 20% of adults and 5% of children with ALL are Ph1 positive(1). In many cases, this karyotypic abnormality involves a more proximal portion of bcr(7), and only 50% of these rearrangements are detected using the standard 5.8 kb bcr region probe(1,7). A small proportion of adults with AML (approximately 2%) are also observed to be Ph1 positive(8), and only one of two cases described had a genomic rearrangement within the region hybridizing to the bcr probe(1).

Bcr-abl analysis seems to be more sensitive than chromosome analysis as a test for CML. As only one type of rearrangement is found in this disorder, bcr-abl analysis can be used instead of karyotype analysis. However, in other leukemias, including ALL and AML, the Philadelphia Chromosome is sometimes present, but many other chromosomal abnormalities exist. Even in those cases which are Ph1 positive, bcr-abl gene rearrangements present are not detected in approximately 50% of the cases when using the standard bcr probe. Thus, bcr-abl analysis should not be used to replace karyotyping in other hematopoietic malignancies. Only in cases suspicious for CML may karyotyping be replaced by bcr-abl analysis.

Costs and Turn-Around Times

Cytogenetics (Routine Chromosome Analysis) - $488.00
Turn-Around Time: 2-3 weeks.
The Genetics Center of Southwest Biomedical Research Institute

Bcr-abl Analysis - $265.00
Turn-Around Time: 5-7 days
Jeff Edman, UCSF
Patients

In the course of a year, the number of specimens submitted for routine chromosome analysis are 0-1 at the SFVAMC, 0-2 at SFGH, and >200 at Moffitt Hospital. A six month period was audited at each of these three hospitals:

Total Chromosome Analysis During This Period: 116
Moffitt Hospital: 116
SFGH: 0
SFVAMC: 0

Of the 116 patients reviewed, two were clinically suspected of having the diagnosis of CML (The remainder included ALL, AML, myelodysplasia, etc.).

The first of these, M.S., is a 40 y.o. male with a peripheral WBC of 136K and marked granulocytic hyperplasia on bone marrow examination. Bcr-abl analysis was not performed. Cytogenetics revealed a translocation between chromosomes 9 and 22 resulting in a Philadelphia Chromosome karyotype.

The second patient, CP', is a 31 y.o. white female who presented with a several month history of anorexia and fatigue, splenomegaly, and a peripheral WBC of 620K. The bone marrow biopsy revealed marked granulocytic hyperplasia. The specimen sent for cytogenetics was inadequate, revealing a total of one metaphase having a normal 46XX chromosome pattern, and a repeat analysis was suggested. A bcr-abl analysis was performed and was positive for rearrangement.

Economic Considerations

During the six month period audited, use of bcr-abl analysis alone in these two patients would have resulted in a savings of $711 ($233 in the first case - where it could have replaced karyotyping - and $488 in the second case - where bcr-abl analysis was necessary because of an inadequate specimen being sent for cytogenetics).
Conclusions

Bcr-abl analysis is more sensitive and less expensive than karyotyping as a genetic marker for CML. However, this test is not a replacement for chromosome analysis in hematopoietic disorders other than CML. Appropriate use of this test in lieu of karyotyping in cases of suspected CML will have a slight positive economic impact.

Bibliography


