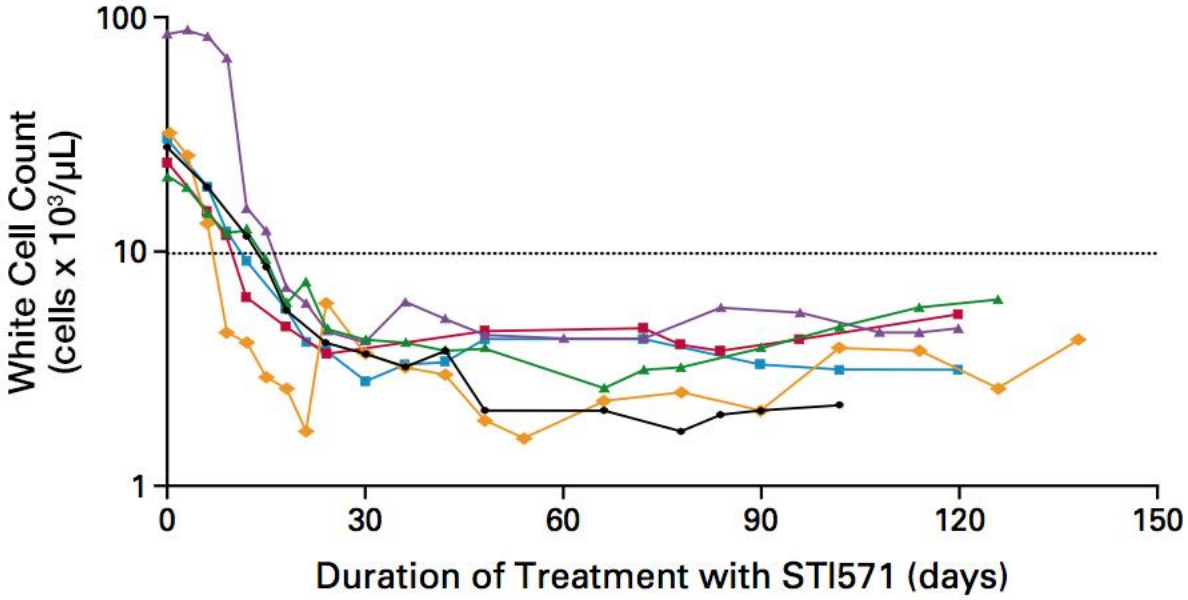
Efficacy of a Treatment for Chronic Myeloid Leukemia

HOW TO USE THIS RESOURCE

Show the figure below to your students along with the caption and background information. The "Interpreting the Graph" and "Discussion Questions" sections provide additional information and suggested questions that you can use to guide a class discussion about the characteristics of the graph and what it shows.



Caption: White blood cell counts in six patients with chronic myeloid leukemia treated with STI571, a drug which blocks the activity of the cancer-causing tyrosine kinase BCR-ABL. Each patient (denoted by a different colored line) received 500 mg of STI571 per day for 150 days. The dotted line represents the upper limit of the normal white blood cell count range.

BACKGROUND INFORMATION

Chronic myeloid leukemia (CML) is a cancer of white blood cells caused by a reciprocal translocation between chromosomes 9 and 22, which means that regions of these two chromosomes are swapped. The translocation brings the *ABL* gene on chromosome 9 next to a portion of the *BCR* gene on chromosome 22 to create a fusion gene called *BCR-ABL*. The *ABL* gene normally codes for a tyrosine kinase that acts as a switch to turn cell division "on" or "off." When the ABL kinase is activated, it triggers cell division by phosphorylating other proteins using ATP as a substrate. In CML patients, the fusion between *BCR* and *ABL* causes the tyrosine kinase to always be "on." This leads to uncontrolled cell division and an increase in white blood cells. Dr. Brian Druker and colleagues produced a drug called STI571 that turns off *BCR-ABL* activity by fitting into the ATP-binding site of the tyrosine kinase. Bound STI571 prevents ATP from binding, which, in turn, prevents phosphorylation of other proteins that would normally trigger cell division. To test the effectiveness of STI571, the researchers gave the drug to 83 patients with CML who had not responded to other conventional treatments. The treatment consisted of a daily drug dose, ranging from 25 to 1,000 mg for different groups of patients, while measuring the patients' white blood cell counts. The graph above shows the white blood cell counts of six patients who had received a dose of 500 mg/day of STI171.

INTERPRETING THE GRAPH

The six lines in the graph represent the white blood cell counts of six patients receiving treatment with 500 mg of STI571 over 150 days. The dotted line represents the upper limit of the normal white blood cell count range. At the beginning of the trial, all six patients had white blood cell counts well above the normal range. Once the treatment started, white blood cell counts rapidly declined, entering the normal range during the first 30 days of treatment. Patients' white blood cell counts remained within the normal range for the duration of treatment. Dr. Druker and colleagues have shown that in 98% of patients treated with 300 mg/day or more of STI571, white blood cell counts decreased to a normal range within four weeks.

Teacher Tip: Prompt your students to explain the parts of the graph as applicable:

- Graph Type: Line graph
- *X*-Axis: Time in days
- *Y*-Axis: White-cell count (# cells × 10^3/ml)
- Dotted Line: The upper limit of normal white-cell count in blood.

DISCUSSION QUESTIONS

- Describe the overall trend that you see in this graph.
- What do the initial values at time zero indicate about the health of the patients? Use the dotted line as a reference.
- How do the trends of the lines from 0 to 30 days compare to the trends of the lines from 30 days to 150 days? Comparing these trends, what claim could you make about the patients' response to the drug?
- Why does the graph show six patients over 150 days and not just one patient? Or all 83 patients?
- Compare the general range of cell counts for all six patients at 0 days, 30 days, 60 days, 90 days, and 120 days. What does this tell you about individual responses to treatment?
- Would you be willing to approve this drug for treatment of other patients based on the results for six patients in this graph alone? What additional evidence would you want to see?

SOURCE

Figure 1 from:
Brian J. Druker, *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. 2001. *New England Journal of Medicine*. 344(14): 1031-1037.
View Paper: http://www.nejm.org/doi/full/10.1056/NEJM200104053441401

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