7.7: The “Poster Boy” of Genetic Research Leading to a Cancer Treatment – Gleevec™ (Imatinib)

13.7.1 Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia (CML) is a type of cancer of white blood cells, myeloid cells, that are mutated and proliferate uncontrollably through three stages (chronic, accelerated, and blast crisis) and lead eventually to death. Cytogenetics showed the myeloid cells of CML patients usually also have a consistent chromosome translocation (the mutant event) between the long arms of chromosomes 9 and 22, t(9:22)(q34;q11). It is also known as the Philadelphia chromosome (Ph⁰). This translocation involves breaks in two genes, c-abl and bcr, on chromosomes 9 and 22, respectively. The fusion of the translocation breaks result in a chimeric gene, called bcr-abl, that contains exons 1 and/or 2 from bcr (this varies from patient to patient) and 2-11 from abl and it produces a chimeric protein (BCR-ABL or p185⁰bcr-abl) that is transcribed like bcr and contains abl enzyme sequences. This chimeric protein has a tyrosine-kinase from the abl gene sequences that is unique to the CML mutant cell. The consistent, unregulated expression of this gene and its kinase product causes activation of a variety of intracellular signaling pathways, promoting the uncontrolled proliferative and survival properties of CML cells (the cancer). Thus the BCR-ABL tyrosine kinase enzyme exists only in cancer cells (and not in healthy cells) and a drug that inhibits this activity could be used to target and prevent the uncontrolled growth of the cancerous CML cells.

13.7.2 Inhibiting the Bcr-Abl tyrosine kinase activity

Knowing that the kinase activity was the key to treatment, pharmaceutical companies screened chemical libraries of potential kinase inhibitory compounds. After initially finding low potency inhibitors, a relationship between structure and activity suggested other compounds that were optimized to inhibit the BCR-ABL tyrosine kinase activity. The lead
compound was STI571, now called Gleevec™ or imatinib (Figure 13.9). This drug was shown to inhibit the BCR-ABL tyrosine kinase activity and to inhibit CML cell proliferation \textit{in vitro} and \textit{in vivo}. Gleevec™ works via targeted therapy—only the kinase activity in cancer cells was targeted and thereby killed through the drug's action. In this regard, Gleevec™ was one of the first cancer therapies to show the potential for this type of targeted action. It was dependent upon the genetic identification of the cause and protein target and is often cited as a paradigm for genetic research in cancer therapeutics.

\begin{figure}[h]
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\includegraphics[width=0.5\textwidth]{biochemical_structure_of_gleevec_imatinib.png}
\caption{Biochemical structure of Gleevec™ or Imatinib. (Wikipedia-Fuse809-CC:AN)}
\end{figure}

13.7.3 Caution

This is a simplified presentation of the CML/cancer targeting by the drug Gleevec™. There are many more details than could be presented here. It is represents as a model of finding a drug for each type of cancer, rather than the one, single "magic bullet" that kills all cancers. Remember, there are always complexities in this type of research to treatment process, such as patient genetic and environmental variation that leads to differences in drug metabolism, uptake, and binding. Also, changes in drug dose, mutation of the \textit{bcr-abl} gene, and other events can affect the effectiveness of the treatment and the relapse rate. Biological systems are extremely complex and difficult to modulate in the specific, targeted manner necessary to treat cancer ideally.

Remember, the drug, Gleevec™, is not a cure, but only a treatment. It prevents the uncontrolled proliferation of the CML cells, but doesn’t kill them directly. The arrested cells will die eventually, but there is always a small pool of CML cells that will proliferate if the drug is discontinued. While sustained use of this expensive drug is beneficial to the pharmaceutical companies, it is certainly not the ideal situation for the patient.

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