THE CANCER TREATMENT REVOLUTION

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A revolution in cancer drug therapy has been brewing for the past twenty years. The three decades of clinical research carried out between 1955 and 1985 were largely devoted to the discovery and clinical trials of combinations of DNA-damaging agents that might best be described as carpet-bombing therapeutics. Great strides were made with these agents in certain diseases such as the hematological malignancies (particularly childhood leukemia), Hodgkin's lymphoma, and the malignancies of the head and neck, colorectum, ovaries and testes and, to a certain extent, breast cancer. But the major epithelial cancers, including lung, colon and prostate, remain largely recalcitrant. Melanomas, pancreatic, hepatic, and brain cancers and most sarcomas are also generally unresponsive, while the toxic/therapeutic ratios of the broadly active carpet-bombing drugs are problematic. A new paradigm is sorely needed.

Hope that a better concept of cancer therapy might emerge began to be appreciated in the 1970s and 1980s. Evidence gathered by several laboratories demonstrated the correctness of the century-old postulate of Theodor Boveri that cancer is due to chromosome injury (1). Indeed, cancer is the commonest acquired disorder of the human genome. Weinberg and his colleagues showed that the disease can be induced by nuclear transfer from a cancer cell to a normal cell (2). And despite the widespread chromosome damage observed in most epithelial cancer cells, Weinberg's (3) and Leder's (4) groups provided evidence that only a small number of mutations are actually required to induce normal cells to become malignant. In those enormously productive two decades, Bishop (5) and Alt (6) and their coworkers respectively demonstrated that gene amplification of myc and dihyrofolate reductase may cause cancer (neuroblastoma) and resistance to effective anti-cancer therapy (methotrexate), while Korsmeyer (7,8) showed that malignancy is due in part to arrest of the death pathway that disposes of cells encumbered by the DNA injuries that lead to cancer. The central

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role of p53 in the death pathway was also uncovered in that decade by Arnold Levine (9) and others. In the same era, Harold Varmus and Michael Bishop performed the Nobel prize-winning experiments that showed that the Rous sarcoma virus (initially described in 1910) is caused by a gain-of-function mutation of a normal growth regulatory gene (in this case a tyrosine kinase) into a gene they called src. That mutation produces a constantly active and thereby oncogenic tyrosine kinase protein (10,11). They coined the terms "protooncogene" and "oncogene". The cancer-provoking protein products of such mutations are now called "oncoproteins".

This was the scientific background when Dennis Slamon and his colleagues showed that amplification of the Her-2/neu gene, leading to overproduction of normal Her2/neu protein, may flood the cells of about 20 percent of breast cancer patients with an overabundance of this tyrosine kinase member of the large epidermal growth factor receptor (egfr) family (12). The surfeit of oncoprotein drives the cancer, and the cancer may be inhibited by blockade of the protein by means of a monoclonal antibody now known as trastuzumab (Herceptin) (13). This was the first targeted therapy of a single oncoprotein and ushered in the present cancer treatment revolution.

The following case illustrates the present status of the revolution and emphasizes the growing role of small molecule inhibitors of oncoproteins in cancer therapy.

Case Report

Ken, a married salesman and father of two, was 49 years old in 1998 and in excellent physical shape. He had been a star wrestler in high school and had the squat, powerful build of the breed.

In the fall of that year, Ken noted progressive fatigue and dyspnea on climbing stairs. He was found to be anemic. No bleeding point was found; his anemia worsened; and red cell transfusions were initiated. After a year of periodic transfusions, he suddenly developed excruciating abdominal pain. Exploratory laparotomy revealed a grapefruit sized mass that had eroded the small bowel and then ruptured. Tumor cells as well as bacteria had been spread through the peritoneum. The pathologic diagnosis was gastrointestinal stromal tumor (GIST), a sarcoma of the Cajal cells (the latter described a century ago by Ramon y Cajal) that control intestinal motility. After a stormy course involving episodes of intestinal obstruction, dumping syndrome, thrombophlebitis and pulmonary embolism, Ken finally began to regain his

health. His anemia resolved, but he recognized that he harbored multiple nidi of GISTs that would surely regrow and destroy him.

Having been informed by his physicians and by the Internet that there was no effective treatment for GIST other than surgery, Ken decided to seek help from Dr. George Demetri at the Dana-Farber Cancer Institute, who was beginning to attack the GIST problem as a high priority. By the year 2000, PET scanning revealed at least 40 GIST tumors studding Ken's peritoneum.

Discovery of an effective treatment of GIST became possible when Varmus and Bishop described the src oncogene (10,11). When they received the Nobel Prize in 1989, Bishop pointed out that at least 25 protooncogenes (the normal precursors of oncogenes) had been identified to date. One of these was kit and another abl, both tyrosine kinases. The mutated and oncogenic forms of abl (either v-abl or bcr-abl) are respectively responsible for a fatal murine lymphoma and human chronic myelogenous leukemia (CML) (14).

Two lines of research effort stemming from those discoveries then combined to come to Ken's aid. The first effort involving abl started in the 1980s and depended upon a decision by Ciba-Geigy (later Novartis) to explore drugs that might inhibit mutant tyrosine kinases. To screen their large libraries for suppressors of tyrosine kinases, they required a monitor of such activity. This they received from Thomas Roberts at Dana-Farber who had fashioned the 4G10 antibody that binds avidly to phosphotyrosine (15). Novartis utilized the antibody in an automated screen in which platelet derived growth factor receptor (PDGFR) was the target tyrosine kinase. The Novartis team (16) came up with Gleevec (imatinib). Fortunately, Brian Druker, a bright physician and a fellow at Dana-Farber, had decided to take his research training in Roberts' laboratory in the early 1980s. He learned that Gleevec inhibits, bcr-abl as well as PDGFR and struggled to persuade Novartis to give him some drug to test whether Gleevec would kill CML cells. Finally the company agreed, and Druker, now at Oregon University School of Health Sciences, Charles Sawyers at UCLA, and their colleagues clearly demonstrated that Gleevec produces long remissions in chronic myelogenous leukemia (14,17). That superb clinical research, first published in 2001, electrified the field and the international media.

The second line of research involved kit. In the 1990s, Swedish investigators studying human fetal gut showed that human Cajal cells express high levels of kit tyrosine kinase activity (18). In the same decade, Allan Bernstein, now the Director of the Canadian Institutes of Health Research, demonstrated that mice deficient in kit have very

few Cajal cells, and those cells function poorly (19). Two key experiments conducted half a world apart by Kitamura's group in Osaka, Japan (20) and Marcia Lux, then a medical student, and Jon Fletcher and their colleagues at the Brigham and Women's Hospital in Boston showed that GISTs are largely due to activation mutations of one copy of a kit gene in an originating Cajal cell (21). George Demetri, having learned that Gleevec inhibits abl, PDGFR and kit, led a team including Brian Druker and others to treat GIST patients with Gleevec (22,23). The excellent response to treatment by the first patient was published in the same issue of the New England Journal of Medicine as were the results of Gleevec management of CML.

This was an event that turned Ken into a poster boy for targeted cancer therapy. He rapidly responded to Gleevec treatment and maintained his remission for two years until 2002. He was pictured in the New York Times undergoing a PET scan evaluation. But cancer therapy is not that simple. Single agent therapy is unlikely to be successful for very long because the emergence of resistant strains of tumor cells is almost the rule in such circumstances. Only combination therapy using different types of drugs that attack a target at different sites on a molecule or attack other key molecules can prevent resistance in most cases.

In explorations of the nature of Gleevec resistance, George Daley (24) and Charles Sawyers (25,26), adopting unique approaches, found that the emergence of Gleevec resistance in bcr-abl driven CML cells is due to a limited number of further amino acid substitutions in the pocket within the abl oncoprotein into which ATP enters to phosphorylate a neighboring tyrosine and begin the activation of the enzyme. Gleevec works by sliding into that pocket and preventing access by ATP. The further pocket mutations prevent Gleevec from sliding in, but permit ATP to enter. The enzyme is once again active.

Here the story shifts back to the pharmaceutical companies and their screening capacity. In the past three years, Novartis, Sugen, Bristol Myers-Squibb and SGX, a new small company, have produced drugs that can enter the kinase domain pocket of the bcr—abl protein even when its amino acids are mutated. Such drugs overcome imatinib resistance in CML. They are likely to be more toxic, but CML patients with imatinib resistance are now doing extremely well. It remains likely that a combination of compounds with different sites of attack on the offending kinase molecule will be required.

Sadly none of these new drugs worked for Ken and his mutated kit gene. They were effective in cell cultures but not in the patient. Side effects including severe depression characterized two of them. Ken had

several more years of quality life than anyone would have expected when his diagnosis was initially made, but he eventually succumbed to the tumor.

Though Ken's life was not saved, his story clearly demonstrates that a cancer treatment revolution is beginning. It is not in full spate because more drugs are needed, and more understanding of the precise genetic abnormalities that drive other more common tumors must be gathered. But the way forward is obvious. To treat the common solid tumors we must understand their genetic drivers and then produce the drug that blocks the oncoproteins on which the cancer cells depend for their survival. In addition, we have to find drugs that will repair the broken death pathway that characterizes cancer cells. All of these goals are presently passing through the pipeline of research. In the next twenty years, it is reasonable to expect that the common cancers will be converted to chronic diseases held in check by combinations of effective targeted drugs. To paraphrase Churchill, "we are not at the beginning of the end, but we are surely at the end of the beginning."

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DISCUSSION

Billings, Baton Rouge: David, I have a patient who is 45-years-old, who has been in remission from acute myelomonocytic leukemia for four years now and for the last two, bone marrows, which have been done at six month intervals, show a wildly abnormal karyotype with greater than 12 lines which are mutated and one normal line in there. Her CBC is normal. Her blood chemistries are normal. She, for all intents and purposes, phenotypically is normal, but I am scared to death that in the next six months, twelve months, eighteen months, she will relapse. Are there agents that you are aware of that she should be receiving in hopes of converting her karyotype into a normal one?

Nathan, Boston: What's happened here is therapy-related. She has developed another clonal disorder. I take it this was a patient who was not treated with a bone marrow transplant.

Billings: No.

Nathan: One of the problems with blunderbuss chemotherapy is that it damages every stem cell in the marrow. Its not a safe treatment. It worked for this patient, gave her a wonderful remission, but it damaged more stem cells in the marrow, and now they are growing up showing this chromosomal disturbance. The diagnosis is myelodysplasia. There is one hopeful note. Patients with myelodysplasia and such clonal abnormalities in their marrows with terrible chromosomes may be stable for long periods of time. You don't know when its going to explode into frank leukemia. Bad chromosomes do not mean that leukemia will emerge tomorrow. Another hit is often required, and the other hit has yet to come. In other words, there has to be another mutation. I know it looks terrible. A search is on for mutant protein kinases in these syndromes with the hope that kinase inhibitors may help them. I am being evasive because the drugs that hit some of those kinases have not been terribly effective yet, but there is some treatment that is possible. The other point is, I don't know how old the patient is, but this is a candidate for marrow transplant.

Billings: She's 45.

Nathan: Well then she's a candidate. That is what I would do in that situation. Start looking for donors, because I think its going to be very difficult to get rid of these bad cells.

Billings: Would you urge her to transplantation prior to her relapse or would you wait for her to relapse?

Nathan: I would not wait. I know it's going to happen. If I were her, I'd probably do it, but some would say wait until that first blast shows up in the peripheral blood or the first nucleated red cell in the peripheral blood, the first sign of marrow invasion. It depends upon how confident you are in the marrow transplant procedure. She's had a lot of chemotherapy. She could get badly injured from the transplant, no question about it, but that's the only way to treat her effectively right now today.

Billings: I'll send you her karyotype.

McKee, Oklahoma City: David, what do you forecast in terms of the continuing revolution with respect to the cross talk between the parenchymal cancer cell and the stromal cell? That's seems to be an area that is attracting enormous attention now. What are your thoughts about that?

Nathan: Some of the leading work on that in breast cancer has been done by a woman named Nellie Polyak in Boston and in other places. There is no question that Nellie has shown that in-situ carcinoma incites gene change in the stromal cells of the breast that induce them to extrude growth factors that are acting back on the cancer cells. Thus, the cancer is the inducer putting out factors that are inducing stromal cells to be supportive of the cancer itself. It's a loop. There has been very little work done in that except in the attempt to deal with blood vessel control. Many tumor cells put out a signal that encourages the tumor vessels to come in to support the tumor. This is Judd Folkman's contribution which is so important. I don't think we are going to solve the cancer problem by attacking its environment. I think the main actor is still the cancer cells, and we need to find the drugs to kill them, and if we do that, the stromal cells and blood vessels won't come in to feed the tumor. I think it is somewhat circular to say that we are going to attack the cancer by depriving it of something from the environment. I think the cancer cell will ride over that and keep on growing. That's my own view.