A Retrospective: On Clinical Studies with 5-Fluorouracil

V. Craig Jordan

See related article by Curreri et al., Cancer Res 1958:18: 478–484.

The 1950s saw the rise of rational drug design to target DNA synthesis in cancer cells. The concept was simple; cancer was replicating uncontrolled compared with normal tissues, so this characteristic was to be its vulnerability. The momentum for rational drug design targeting DNA increased with the study by Watson and Crick of the structure and simplicity of DNA (1). The scene was set to cure cancer during the remaining years of the 20th century.

The target for 5-fluorouracil (5FU) is thymidylate synthetase, and the goal of the targeted therapy is to create a thymine-less state. Without available thymine to be incorporated into DNA, this would be toxic to rapidly dividing cancer cells. However, 5FU is not active itself and must first be activated by conversion to the nucleotide deoxyuridine monophosphate (5-FdUMP), which now allows appropriate targeting to thymidylate synthase. In addition, a reduced folate cofactor is required for tight binding of the inhibitor to thymidylate synthetase. The natural substrate is N5,10- methylenetetrahydrofolic acid, which binds covalently to 5-FdUMP (2). As a result, the enzyme is neutralized.

The clinical development program for 5FU, combining the McArdle Laboratory, the Clinical Oncology Group at the University of Wisconsin Hospital, and Hoffman-LaRoche, was, on the face of it, traditional (3), except that 5FU went forward to clinical testing without initially obtaining a patent! The group of investigators wanted to move forward rapidly without administrative delays. This was a bold and altruistic clinical program with the plan to aid patients as rapidly as possible. Only later did nucleotide preparations obtain patent protection. The first major clinical findings were significant.

A total of 103 cases were reported of all sorts of solid tumors, leukemias, and lymphomas. Heidelberger synthesized 5FU (4, 5), Hoffman-LaRoche prepared the administered medicine, and Dr. Antoni Curreri led the clinical team. Results were definitive and important for future integration of 5FU into the standard treatment regimens for breast and colon cancer. Several conclusions deserve mention (3). Analgesics were no longer required for the relief of pain in the majority of patients following treatment with 5FU. The objective response rate was 25% in patients receiving what they considered an adequate therapeutic dosage, but regressions were noted only in those patients manifesting severe toxicity. Finally, patients with solid tumors that responded to repeated courses of 5FU did not develop resistance. So, 5FU was destined to join methotrexate that prevents purine synthesis by blocking the enzyme dihydrofolate reductase and alkylating agents like the prodrug cyclophosphamide, which alkylates the "double helix" (1).

Strategies for the treatment of breast cancer were simultaneously evolving in two directions. First, combination cytotoxic chemotherapy was proven to be effective to create cures in childhood leukemia, so using combination chemotherapy for the treatment of solid tumors to hit multiple targets, kill optimally, and retard the development of drug resistance seemed prudent. The late Gianni Bonadonna tells the story in his Karnofsky Memorial Lecture (6) that in May 1972, he met Paul P. Carbone at the NCI, who showed him the remarkable response rate of combination cyclophosphamide, methotrexate, 5FU, and prednisone (CMFP) in metastatic breast cancer. There were 2% complete remissions and 40% partial remissions with a median duration of response of 8 months (6). Bonadonna, with the full support of Pietro Buscalossi and Umberto Veronesi, repeated the CMF regimen in metastatic breast cancer but deleted the P, obtaining a 57% response rate (6). This, now the classic CMF regimen, was used successfully to treat metastatic disease. Second, the major conceptual advance was the use of combination cytotoxic chemotherapy as an adjuvant following surgery to destroy scattered subclinical micrometastases. Bonadonna’s first report (7) demonstrated that treatment failure occurred in 24% of 176 control patients but in only 5.3% of 207 women given combination chemotherapy after 27 months. Bonadonna’s update in his Karnofsky lecture (6) demonstrated that the relapse-free survival of 109 months and total survival was not yet achieved and was extraordinarily large in premenopausal patients at 14 years. These data were compared with postmenopausal patients with a relapse-free survival and overall survival of 43 months and 36 months, respectively. These advances in clinical care would not have occurred but for the era of rational drug design to target the mechanisms of cell replication through DNA synthesis. 5FU was a pivotal cornerstone in that story. However, it was a strategy that was destined to fail because of a lack of tumor specificity. Normal replicating cells were equally vulnerable to inhibitors of DNA synthesis, with severe side effects and toxicity in the colon and hematologic disorders with immune suppression. Changes had to occur, and the Director of the McArdle Laboratory, Harold Rusc, was to play a prominent role in catalyzing the change to tumor-targeted therapy. Harold Rusc had a vision to create the premier Cancer Research Center in America and discover the causes of cancer. He succeeded with Howard Temin with reverse transcriptase (and the Nobel Prize), Jim and Betty Miller with chemical carcinogenesis, and many others. But it was Heidelberger who was the outlier to create a rational therapy of practical value to treat cancer.

I did not know Charles Heidelberger, but I had the honor to attend his memorial service in Madison, Wisconsin, following...
his death on January 18, 1983, at the age of 63 years. On that occasion, I met patients who had, to that point, survived their breast cancer thanks to Charles Heidelberger. What I was not aware of, at that time, was why Harold Rusch and Paul Carbone had approved my recruitment so rapidly to the Wisconsin Clinical Cancer Center when this was proposed by Doug Tormey and David Rose in 1977. In 1974, Harold Rusch was the Director of the McArthur Laboratory for Cancer Research (8) when he was told that his daughter Judy had breast cancer. Dr. Curreri confirmed the diagnosis, and a modified radical mastectomy was performed at Evanston Hospital, Illinois, near Judy’s home. The prognosis was bleak, with 23 positive axillary lymph nodes involved. Fred Ansfield, back in Wisconsin, with his faith in chemotherapy was optimistic, and Judy came to Madison to start courses of combination chemotherapy but to no avail. Judy died on August 23, 1976.

Harold Rusch was a great man who walked with Presidents. He said that he had doubts that he had not spent more time considering the treatment of cancer rather than the cause. He was angry and depressed at the unanticipated turn of events in his life. I was unaware of the burden he was carrying in 1977 when I spent 3 months at the Wisconsin Clinical Cancer Center and he asked me to tell him all about tamoxifen and my strategy to create a long-term adjuvant targeted therapy for the treatment of breast cancer (9). Tamoxifen, at that time, was not even FDA approved for the treatment of metastatic breast cancer in the United States of America. That landmark was only to occur on December 29, 1977. I was recruited by Paul Carbone and Harold to come to the brand new Wisconsin Clinical Cancer Center in 1980. Harold and I had offices next to each other and I was mentored by him each day in techniques of leadership in Cancer Centers. We were friends, but when he was diagnosed with prostate cancer, Harold prepared for his memorial service. I was truly honored to be one of those invited to speak at Harold’s memorial service. I took the initiative to write to President Ronald Reagan to request a letter recognizing the extraordinary contributions of Harold Rusch as a leader in cancer research for our nation. He was given the citation by Chancellor Donna Shalala and me at his home, just before he died on May 26, 1988. I chose to read the letter from the President at Harold’s memorial service.

Through the leadership skill of Harold Rusch [Director of the McArdle Laboratory (1946–72), Director of the Wisconsin Comprehensive Cancer Center (1972–1978), President of the AACR (1954), and Editor-in-Chief of Cancer Research (1950–64)], medicine moved from rational drug design to disrupt DNA synthesis (3–5) to the first targeted therapy for the treatment and prevention of breast cancer (9). I was subsequently invited to write a retrospective of Harold’s contribution in advancing cancer research, which I was honored to do. It is entitled “Harold P. Rusch, MD and the UW Madison – A Tale of Two Cancer Centers” (10). 5FU, the initial success story in the treatment of cancer at Wisconsin, passed the baton 25 years later to the development of tamoxifen, the first target treatment and preventive for any cancer (9). The progress with tamoxifen at Wisconsin to save lives is a result of the opportunities immediately recognized by Paul Carbone and Harold Rusch once the “War on Cancer” had been declared.

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References
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