High-dose chemotherapies (hdc) and stamp as cancer treatment

STAMP

Since the 1960s, high-dose chemotherapies (HDC) had been successful in curing acute leukemia and Hodgkin’s disease, but not that successful in curing solid tumors such as lung cancer and breast cancer. Chemotherapists were now wondering whether by increasing the power of the dosage, they could make HDC effective for treating solid cancer. But for most chemotherapy drugs, the dose limit depended on the bone marrow. How can one increase the drug dosage by five or ten times without destroying the bone marrow?

Bone Marrow Transplantation

In the late 1960s, Donnall Thomas had shown that bone marrow could be harvested from one patient and transplanted back – either to the same patient (called autologous transplantation) or into another patient (called allogeneic transplantation).

Allogeneic bone marrow transplantation was tricky, often deadly. It could lead to a deadly complication called graft-versus-host disease if the foreign marrow turned and attacked the body of the recipient. Autologous bone marrow transplantation (ABMT), on the other hand, was less risky. Here, the patient’s own marrow was harvested, frozen, and transplanted back into his body.

STAMP

By harvesting and freezing bone marrow, then implanting the marrow after HDC, doctors were theoretically able to break through the limit of toxicity;

the so-called “ red ceiling”. It was now possible to give five- or even tenfold the typical doses of drugs.

Among the first proponent of this strategy was Emil Frie, who was now the director of Farber’s institute. By early 1980s, Fred had convinced himself that a high dose chemotherapy combined with autologous bone marrow transplantation (HDC/ABMT), was the only conceivable solution in cancer therapy. He called this protocol “ Solid Tumor Autologous Marrow Program”, or STAMP. To develop this protocol, Frei recruited William Peters as a fellow at the institute in 1982. By December 1984, 32 women had completed the Phase I study of the regimen, designed to investigate safety. The researchers proceeded with Phase II trials, which showed very promising results. But randomized controlled trials (Phase III) were needed to confirm the benefit of STAMP. In 1985, William Peters left the Faber institute to set up the trial at Duke University in North Carolina. He also persuaded the Cancer and Leukemia Group B (CALGB) to sponsor a multi-center, randomized controlled trial.

AIDS

In March 1981, a team of doctors reported eight cases of Kaposi’s sarcoma in a cohort of men in New York. All eight of the men were homosexual. One of the men was also diagnosed with a rare pneumonia called PCP, which only occurs in humans when the immune system is severely compromised. Between June and August 1981, additional clusters of PCP, cryptococcal meningitis, Kaposi’s sarcoma, and rare lymphomas were reported in young men in cities throughout America. The common pattern behind all these

diseases, aside from their bias towards gay men, was a total collapse of the immune system. A letter in Lancet called the disease “ gay compromise syndrome.” Others called it GRID (gay-related immune deficiency). In July 1982, it was called acquired immuno-deficiency syndrome, or AIDS.

In January 1983, Luc Montagnier, a virologist at the Institut Pasteur in Paris, discovered a virus in a lymph node biopsy from a young gay man with Kaposi’s sarcoma. Montagnier soon deduced that this was an RNA virus that could convert its genes into DNA and lodge into the human genome-a retrovirus. He called his virus IDAV, immuno-deficiency associated viruses, arguing that it was likely the cause of AIDS. Montagnier’s discovery was corroborated in the spring of 1984 by Robert Gallo at the National Cancer Institute. Margaret Heckler, the Health and Human Services secretary, made this discovery public in the spring of 1984. “ We hope to have a vaccine ready for testing in about two years,” she said.

But AIDS activists, facing an epidemic that was decimating their community, could not afford to wait. In the spring of 1987, a group of volunteers form a group named the AIDS Coalition to Unleash Power, or ACT UP. Led by a writer named Larry Kramer, ACT UP promised to transform the landscape of AIDS treatment using a kind of militant activism unprecedented in the history of medicine.

The Map and the Parachute

While William Peters was investigating the efficacy of the STAMP protocol, many oncologists had long assumed that the regimen was so effective that no trial would be needed. By the late 1980s, hospitals and private clinics

offering high dose bone marrow transplantation (HDC/ABMT) for breast cancer had sprouted up all around the US, UK, and France.

Insurance and Litigation

Costs from $50, 000 to $400, 000 per patient, HDC/ABMT is an expensive therapy. Health maintenance organizations (HMO's), a popular form of health insurance in America, had refused to pay for these therapies because they regarded them as experimental and investigational. However, this would change after the landmark case, Fox v. Health Net in 1993.

In 1991, a 38-year-old public-school teacher named Nelene Fox was diagnosed with breast cancer. She requested Health Net, her HMO, to pay for HDC/ABMT to treat her cancer. Health Net declined her request, stating this therapy was an unproven, experimental therapy. Fox's brother, an attorney named Mark Hiepler, took Health Net to court. By the summer of 1992, when Health Net refused yet another request for coverage, Fox went ahead with the therapy on her own. By then she had raised $220, 000. On April 22, 1993, less than a year after the therapy, Fox died. Mark Hiepler sought damages from Health Net for delaying his sister's treatment. The crux of his case rested on the definition of the word " investigational." HDC/ABMT could, he argued, hardly be considered an " investigational" procedure if every major clinics in the nation was offering it to patients. On December 28, 1993, a Californian jury awarded Fox's family $89 million.

In late 1993, because of the lobbying efforts from a 47-year-old cancer patient named Charlotte Turner, the state of Massachusetts mandated coverage for HDC/BMT for eligible patients within the state. By the mid-

1990s, seven states required HMO’s to pay for HDC/ABMT, with similar legislation pending in seven other states. Between 1988 and 2002, 86 cases were filed against HMO’s that had refused to pay for transplants, of which 47 were successful.

Research Misconduct

Werner Bezwoda, an oncologist at the University of Witwatersrand in Johannesburg, South Africa was one of the most prominent and successful HDC/ABMT therapists. In May 1999, Werner Bezwoda presented his results at the annual meeting of the American College of Clinical Oncology in Atlanta. His results were spectacular: Eight and a half years after HDC/ABMT, 60% of his patients were alive, whereas only 20% survived in the control group.

In contrast, the results presented from three other trials in the afternoon were not good. In one study, the researchers found “ not even a modest improvement,” and complication rates considerably higher than the control arm.

How do one reconcile these disparate results? In December 1999, a team of researchers flew off to South Africa to take a look at Bezwoda’s data. Upon arrival, they requested the log books for the 158 patients Bezwoda reported treating. He gave them log books for 58 and said the rest had been lost. The data he gave them was shoddy. Many records had unsigned, handwritten entries and there was no evidence that Bezwoda had randomly assigned patients. There were no records showing that any patients had received the standard treatment. One of Bezwoda’s purported breast cancer patients was

actually a man. The entire thing had been a sham. Bezwoda’s protocol was completely fabricated and the whole thing was a fraud.

A Final STAMP Trial

In the summer of 1999, a final trial was designed to investigate whether STAMP might increase survival among patients with metastatic breast cancer. Results came in four years later: There was no discernible benefit.

Cancer Undefeated

In May 1997, eleven years after the 1986 Bailar-Smith analysis, Bailar was back with another appraisal of the progress on cancer. His article, entitled “ Cancer Undefeated,” depicted the War on Cancer as a dynamic, moving battle against a dynamic, moving target.

Between 1970 and 1994, cancer mortality had increased by about 6 percent, from 189 deaths per 100, 000 to 201 deaths. Cancer mortality had increased among people over 55, but decreased by the same proportion among people under 55.

Death rates from colon cancer, cervical and uterine cancer had decreased, mostly due to earlier detections (colonoscopy and Pap smears). Death rates for most forms of children’s cancer, Hodgkin’s disease and testicular cancer had also declined.

Lung cancer was still the biggest killer, responsible for 25 percent of all cancer deaths. Overall death rates had increased by 6 percent. Death rates among men had peaked and dropped off by the mid-1980s, while death

rates among women over the age of 55 had increased by 400 percent. The incidence of lung cancer was highest in people older than 55 and was lower in people under 55.