



Dr. Alan Yagoda and the Development of Systemic Therapy for Advanced Bladder Cancer

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Advances in cancer chemotherapy for genitourinary tumors lagged behind those for other cancers such as the hematologic malignancies. Chemotherapeutic agents with activity against lymphoma and leukemia were discovered as early as the 1940s. Yet, it was not until 15-20 years later that actinomycin-D was shown to have activity against Wilms tumor and testicular tumors.¹

In the mid-1980s, Dr. Alan Yagoda and his group at Memorial Sloan Kettering Cancer Center (MSKCC) introduced the concept of combination chemotherapy for the treatment of bladder cancer which became one of the few successful systemic therapies in the treatment of genitourinary (GU) malignancies at the time. This article will provide a brief history of urologic cancer chemotherapy leading up to the time of the introduction of methotrexate, vincristine, adriamycin and cisplatin (M-VAC) with a focus on Dr. Yagoda and his work.

MATERIALS AND METHODS

A literature search was performed using PubMed and conventional search engines on the history of GU oncology, early research on systemic therapies for GU malignancies, and Dr. Alan Yagoda. Further information about Dr. Yagoda was obtained from communications with medical oncologists and urologists who trained and worked with Dr. Yagoda.

EARLY DISCOVERIES IN CANCER CHEMOTHERAPY

Surgical excision was the only identified treatment for cancer before the 1940s. From 1809, when Ephraim McDowell removed an ovarian tumor and showed that surgery could provide a cure for tumor masses, surgery remained the mainstay of cancer treatment.² Given the paucity of successful systemic therapies for GU cancers,

these had been regarded as mostly “surgical diseases.” Indeed, Dr. Willett Whitmore observed that in the 1960s: “it would have been both unnecessary and unrewarding to devote a volume to the *Principles and Management of Urologic Cancer* given that the extent of available information was insufficient to be the subject of a textbook.”³

In 1946-1947, the observation that mustard gas led to leukopenia was published and its subsequent therapeutic use in leukemia and lymphoma served as a seminal event in the development of cancer chemotherapy.⁴ According to Sir Ronald Bodley Scott, before these discoveries, the role of the physician in cancer therapy was [limited] to providing pain relief and comfortable words.⁴ Furthermore, any thought that malignant disease could be controlled, let alone be cured, was simply unfathomable. Yet by the late 1940s, mustard gas showed efficacy against non-Hodgkin Lymphoma, and Sidney Farber demonstrated short-term remissions in patients with leukemia using methotrexate.²

Such discoveries led to an era in which chemotherapy became a therapeutic option. However, in a review of “Historic Milestones in Curative Chemotherapy” published in 1979, GU malignancies were greatly underrepresented.¹ Zubrod¹ lists the chronology of the first curative chemotherapeutic agents discovered from the 1940s to 1960s as (1) alkylating agents, (2) folate antagonists, (3) corticosteroids, (4) mercaptopurine, and (5) actinomycins. The first 4 agents showed activity against the hematologic malignancies. However, success in solid tumors such as GU malignancies was not demonstrated until the emergence of the fifth agent—actinomycin.

In 1956, Farber and his group discovered that actinomycin had clinical activity against metastatic Wilms tumor.¹ Shortly thereafter, in 1960, Li et al published on complete remissions in adult nonseminomatous testicular tumors with actinomycin-D, chlorambucil, and methotrexate.¹ This was one of the first successful systemic chemotherapeutic regimens against a GU malignancy, published more than 10 years after chemotherapeutic successes in hematologic malignancies. In the 1970s, Einhorn et al published extensively on the use of combination chemotherapy in testicular cancer, showing complete remission in some patients.⁵ These milestones marked a period of discovery and growth in the field of GU oncology.

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A SUCCESSFUL CHEMOTHERAPY COMBINATION REGIMEN

In the late 1970s and 1980s, Dr. Yagoda and his group at MSKCC began investigations using cisplatin in patients with advanced urothelial cell carcinoma. In a 1984 update on the *Progress in Chemotherapy for Cancers of the Urothelium*, Dr. Yagoda writes “data suggesting cisplatin had significant antitumor activity against transitional cell carcinoma of the urothelium led to renewed interest by medical oncologists and urologists in the use of cytotoxic chemotherapy for advanced bladder cancer.”⁶

In that same review, Dr. Yagoda noted that since 1976, many new investigational drugs had emerged; however, these lacked systematic studies and needed to be examined in single-agent disease-oriented phase II trials.⁶ Over the next decade, his group accomplished exactly that. In 1988, Dr. Cora Sternberg from the group published data on the use of cisplatin, methotrexate, doxorubicin (adriamycin), and vincristine independently and in combination. These had proven the most valuable single agents with complete and partial remission rates of 30%, 29%, 17%, and 18%, respectively.⁷ However, these were mostly partial responses, and survival was in the 12-month range. Their efforts in evaluating single agents led to a series of trials investigating several combinations. The group subsequently combined the 2 most active regimens (methotrexate + vincristine and cisplatin + adriamycin) into the 4-drug M-VAC regimen.

The initial data showed that the M-VAC regimen induced a complete response in 37% of cases with an overall response rate of 69% and a median response of duration exceeding 9.5 months.⁷ This combination chemotherapy regimen became the standard therapy for patients with advanced urothelial carcinoma.

DR. ALAN YAGODA

Dr. Alan Yagoda was born and raised in Brooklyn, NY. He attended the University of Vermont Medical School. Most of his career, he worked and taught at MSKCC where he became Chief of the Solid Tumor Service. However, owing to disagreement with the chief of medicine, Dr. Yagoda decided to leave. He joined the Columbia University College of Physicians and Surgeons in 1991, where he continued as a prominent researcher and dedicated mentor. He authored more than 100 journal articles and 70 book chapters covering all GU malignancies. A dedicated physician, brilliant scientist, and eccentric mentor Dr. Yagoda led numerous investigations for systemic therapies to treat cancers of the testes, bladder, kidneys, and prostate with a special interest in bladder cancer. Through his systematic and rigorous research methods, his group introduced the first successful systemic therapy for advanced bladder cancer in the 1980s.

WORKING WITH BRILLIANCE

According to those who worked closely with him, Dr. Yagoda could be a difficult person to work with, “if he

liked you he was great, if not it was a problem.” Dr. Harry Herr recalls “if you worked with him closely, you recognized it and put up with him because scientifically he was practical and fair.” He demanded excellence because he was very bright, but at the same time, he was like the absent-minded professor.

For most people, writing a book chapter is a tedious and formidable task; however, when Dr. Yagoda was involved, this was an entirely different experience. Dr. Herr recounts his experience as a Junior Attending writing a book chapter with Dr. Yagoda. “He was a procrastinator; he approached me on a Thursday or Friday and asked if I would help him with the surgical aspects of a book chapter on genitourinary malignancies. I agreed and he replied ‘It’s due on Monday.’ We boarded ourselves up in his office that weekend, working 16-18 hours/day only going home to sleep. He basically gave a talk without any notes as Isis (his secretary) transcribed everything he said. He talked, paced, yelled and the chapter came out. When something surgical came up I would briefly chime in but then he would quickly take the lead again.”

His secretary Isis took care of all the references; the chapter was ultimately only a couple of weeks late—impressive considering how quickly it was written. Dr. Herr recalls he learned more medical oncology in 1 weekend than he thought possible. His only regret was not recording the session.

Dr. Howard Scher similarly described him as having an “encyclopedic mind.” In a speech given at Dr. Yagoda’s memorial, Dr. Scher⁸ shares “Imagine the feeling of having completed, or so you thought, an exhaustive review of the literature only to encounter him telling you, sight unseen, the articles and pages that you missed.”

He was well established in his field and his work so prolific that even his patients recognized the significance of his contributions. According to Dr. Scher,⁸ 1 patient after reading the literature on his own disease realized that everyone referred to Dr. Yagoda which led him to create a neon sign that read “YAGODA SAYS.” His former fellows recall this sign prominently displayed in his office and observe that only Dr. Yagoda could have such a sign.

His brilliance and eccentricity translated into his speaking style. He was described as an incomparable orator; he had a way of delivering large amounts of information in a uniquely memorable style. Dr. Herr recalls his slides were gray, broken, and outdated, but everything he said was brilliant. Dr. Scher⁸ writes “Several of his classics are not easily translatable to print such as the typical findings on digital rectal examination or the determination of response in penile malignancies.”

RESEARCH METHODS

In a 1989 literature review outlining the research on new cytotoxic single-agent therapies for renal cell carcinoma (RCC) Dr. Yagoda keenly observes “Patient selection,

undoubtedly, has been a critical silent statistician in evaluating the antitumor activity of agents tested against renal cell cancer.” This was referring to the fact that patients with good performance status and minimal disease in lung and lymph nodes seemed more responsive than those with more extensive disease.⁹

In both articles and book chapters, he frequently discussed and emphasized the importance of well-organized and systematic clinical trials to evaluate drugs. He made key observations regarding patient selection, well-defined end points, and the importance of accurate patient staging. He applied these rigorous criteria to his own studies and clinical trials.

In many of his reviews, he discusses the necessary shift from “evaluable” disease parameters to “measurable” parameters.¹⁰ These definitions directed his study designs, and he used information from prior drug-oriented studies to conduct disease-specific phase II trials of the drugs that eventually led to the M-VAC combination. Dr. Daniel Petrylak recalls that he used a systematic approach to testing each drug as “singlets,” then mixing and matching them into “doublets” based on nonoverlapping mechanisms of actions and toxicity profiles. Ultimately, he combined the 2 most successful “doublets,” and the M-VAC regimen emerged.

DR. YAGODA’S LEGACY

His scientific accomplishments were monumental, but his legacy was even more outstanding and reflected by the accomplishments of those he mentored. Those who trained with him described him as brilliant and larger than life. His former fellows remember him fondly and shared some of their most memorable experiences with Dr. Yagoda. Many are principal investigators on major investigative protocols, and quite a few are division chairs or department heads. It is not an exaggeration to say that his former fellows lead the research in areas ranging from prostate cancer to bladder cancer and are all prominent names in GU oncology.

Those who trained with him share what a key figure Dr. Yagoda was to the launching of their careers. Dr. Petrylak recalls how Dr. Yagoda sent him and Dr. Sternberg to present some of the group’s most important work at international conferences. He would tell his fellows “I want you to promote yourselves,” and he would allow the fellows to present the most significant data from the group. In fact, he would even feign illness to send his fellows and Junior Faculty in his stead to present at prominent meetings.

Those he trained remember him fondly and are grateful for the work ethic he modeled and contributions he

shared with them. They describe him as brilliant, kind, and eccentric. It is particularly fascinating that he was a leading oncologist yet he smoked “like a chimney.” He passed away in 1995 from complications of surgery for an abdominal aortic aneurysm. His death was a shock to all who knew him, but his legacy remains strong in his scientific contributions and the careers of those he trained.

CONCLUSION

The last half century has heralded significant advances in systemic treatment for GU cancers. The seminal research in chemotherapy for bladder cancer, and many other GU malignancies, was led by Dr. Alan Yagoda, an enigmatic and brilliant researcher. His achievements and his legacy have contributed to shaping the field of multidisciplinary GU oncology as we recognize it today.

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