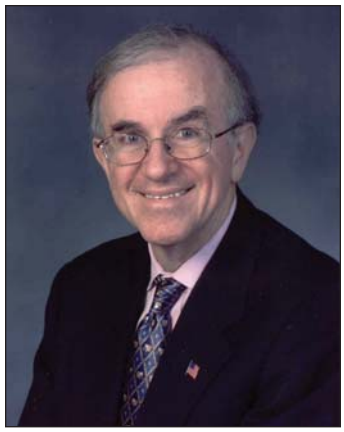
LEGENDS IN UROLOGY



Lawrence H. Einhorn, MD
Lance Armstrong Distinguished Professor of Medicine
Indiana University, Melvin and Bren Simon Cancer Center
Indianapolis, Indiana, USA

I had the distinct honor of being approached by the Canadian Journal of Urology to write a description of my work in testicular cancer for the section *Legends in Urology*. Although one could argue that the pages of this prestigious journal could be better filled with original research, nevertheless, I was flattered with the request and delighted to comply.

I joined the faculty at Indiana University in July 1973. I had the distinct good fortune to strike up an immediate collaboration and long lasting friendship with Dr. John P. Donohue. He had already developed an international reputation as a skilled and thoughtful urological oncologist, especially in the field of testicular cancer. He was among the first to develop the bilateral suprahilar radical lymph node dissection and then, with the advent of platinum combination chemotherapy, he was able to modify this and was one of the first on this continent to do nervesparing RPLNDs.

I never would have had access to a significant patient population with metastatic testicular cancer were it not for our early collaboration. In 1974, we developed our first platinum combination chemotherapy for metastatic disease. During this time, actinomycin-D was the standard treatment with a resultant 5% cure rate. Cisplatin was an experimental drug and we added this to a previously established two drug synergistic regimen, Vinblastine + bleomycin. This was the first platinum combination chemotherapy regimen in the world, not just for testicular cancer, but for any tumor type. Even in my youthful exuberance, I was astonished by the success of this regimen, as we literally had a one log increase in the cure rate going from 5% to between 50% and 60%. With the help and collaboration of Dr. Donohue, we then developed a series of clinical trials, asking relevant questions. We were able to demonstrate that we could reduce the dose of Vinblastine and mitigate the neuromuscular toxicity and myelosuppressive complications. We then challenged one of the basic tenets in medical oncology, namely that in order to have a durable remission, one needed to give remission induction therapy followed by long term maintenance chemotherapy. Therefore, our next randomized phase III study had as a control arm a total of 2 years of Vinblastine therapy and the experimental arm was PVB for 4 courses and just 12 weeks of therapy. This study showed equivalence between the 2 arms and we were able to eliminate that last 21 months of therapy.

We next studied another experimental drug, etoposide (VP-16). We were able to demonstrate single agent activity, but no cures in patients who failed to achieve durable remission with PVB. The combination of cisplatin + etoposide was shown by others to be highly synergistic. We, therefore, did our first salvage chemotherapy regimen with the two drug combination of cisplatin + etoposide. It is noteworthy that neither cisplatin nor etoposide would have any chance of cure as a single agent in this refractory population. We were able to verify the pre-clinical data as we demonstrated a 25% cure rate. This was the first time an adult solid tumor had been reproducibly cured with any form of second-line therapy.

With that as a background, we wanted to address the question of moving etoposide up as first-line therapy. Our next randomized study compared PVB to bleomycin + etoposide + cisplatin (BEP). This phase III study achieved clinically and statistically superior results with the BEP regimen, as well as less neuromuscular toxicity. Therefore,

when this study was completed in 1984, we abandoned PVB as a first-line regimen. Our next study was conducted from 1984 to 1987 and we looked at the majority of the patients who constituted what is referred to as good risk metastatic disease. We were able to attain identical cure rates with 3 courses (9 weeks) of BEP compared to the control arm of 4 courses (12 weeks) of therapy. Thus, from 1974 with the original PVB regimen with 4 courses of therapy, higher dosages of Vinblastine with significant myelosuppressive and neuromuscular toxicity, and 2 years of Vinblastine therapy to 1987, when we completed BEP x 4 versus BEP x 3, we were able to reduce the duration of therapy from 2 years to 9 weeks for the majority of our patients.

Finally, we were the first to demonstrate that one could overcome platinum resistance and have a remarkable 60%-70% cure rate with high dose carboplatin + etoposide in resistant or refractory patients.

Testicular cancer is a unique disease for many different reasons. I would be remiss if I didn't mention the fact that not only is this the most chemo-sensitive and chemo-curable solid tumor, but it is also the most surgically curable even in the presence of metastatic disease. There are few, if any, solid tumors that can be initially cured with a lymph node dissection with positive lymph nodes, even though they are some distance from the primary site. Furthermore, the role of surgery is well established with resection of persistent, enlarged retroperitoneal lymph nodes following chemotherapy, either with the findings of mature teratoma or even with the pathology being germ cell cancer. Salvage surgery can even cure patients who fail to be cured with BEP, have disease localized to the retroperitoneum, and have a rising serum tumor marker.

This has been a wonderful personal journey for me and I had the privilege and honor of sharing this discovery pathway with my friend and colleague, John Donohue. After he retired, I was equally fortunate to have Dr. Richard S. Foster as my colleague in the management of patients with testicular cancer. Andy Warhol once said that everyone is famous for 15 minutes. Fifteen minutes was the length of time that I was allotted during my original plenary session paper at the American Society of Clinical Oncology (ASCO) and that certainly did propel me to a certain degree of fame and recognition. Far more important was the implication of these studies for the young men with testicular cancer. Prior to the advent of cisplatin, the cure rate for testicular cancer was 5%, and at the present time, it is a remarkable 80%.

I wish that we had similar success rates in other metastatic diseases. The story of the cure of metastatic testicular cancer is an encouraging study for clinical researchers involved in new drug development, as well as clinical trials. Hopefully, with the improved knowledge and the basic biology of cancers, I will be able to witness similar success stories in other metastatic tumors as well.

Lawrence H. Einhorn, MD
Lance Armstrong Distinguished Professor of Medicine
Department of Medicine
Division of Hematology/Oncology
Indiana University School of Medicine
Indianapolis, Indiana, USA