Single Agent Versus Combination Chemotherapy

The Editor interviews:
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Editor: One hears more and more about combination chemotherapy for cancer. Is single agent treatment a thing of the past?

Dr. DeVita: Not entirely. Certain types of tumors have demonstrated remarkable responsiveness to single agents. The success of methotrexate in the treatment of choriocarcinoma is well known. Over 70 percent of women can be cured, even if the disease is widely disseminated. Choriocarcinoma’s exquisite responsiveness to single agent therapy may be related, in part, to its rapid proliferation and the host’s ability to mount an effective immune response to what may be allogeneic residual disease. To no small extent, therapy has been aided by the presence of a marker, chorionic gonadotrophin.

Another tumor that is responsive enough to single agent chemotherapy to warrant the word “cure” is Burkitt’s lymphoma; 20 percent of Burkitt’s original patients achieved long-term remission using minimal amounts of cyclophosphamide alone. In a randomized trial of single or multiple high doses of cyclophosphamide conducted by the National Cancer Institute’s unit in Uganda, 10 of 11 patients with localized disease (Stages I or II) have sustained long remissions. Multiple doses of cyclophosphamide were no more effective than single doses in patients with localized disease, but it must be emphasized that multiple doses of this potent immunosuppressive agent failed to do any harm. Relapses were no more
common after six doses than one. On the other hand, multiple doses appear superior to single doses in Stages III and IV, although the overall results in patients with advanced disease were inferior to those with localized disease.

Editor: *Do any common tumors respond to single agent chemotherapy?*

Dr. DeVita: Of the more common tumors, ovarian carcinoma responds well to alkylating agents with over half of patients achieving good responses. Significantly, 20 percent of these responses are complete remissions. In one large study, two-thirds of complete responders remained continuously free of disease for up to nine years. However, drug combinations would be welcome if other active agents can be identified.

Editor: *How effective is the recent use of single agent therapy for malignant islet cell tumor of the pancreas?*

Dr. DeVita: The ultimate role of Streptozotocin is as yet unclear. However, tumor mass was reduced in 48 percent of 29 patients, and 17 percent obtained complete remission. The average duration of remission has been approximately one year. Although data are still preliminary, a median survival time of 744 days for responders versus 289 days for nonresponders suggests that response to this drug prolongs life.

Editor: *What then are the limitations of single agent chemotherapy?*

Dr. DeVita: Complete remissions have been rare with single agents used against solid tumors. For example, Livingston and Carter evaluated 1,590 breast cancer patients treated with single agents. While the overall response rate averaged 30 percent, only one complete remission was observed. Furthermore, the duration of remissions achieved with single agents has generally been short; in acute lymphatic leukemia, remissions induced with methotrexate, prednisone or vincristine lasted an average of 45 days. This phenomenon is often referred to as the “iceberg effect.” Single agents may reduce the tumor population from 10^10 to 10^8 with apparent complete remission, but after only a few doublings, the cells rapidly resurface to pretreatment levels.

Editor: *The magnitude of cell proliferation is often difficult to perceive.*

Dr. DeVita: Yes. Perhaps the best method to describe the quantitative aspects of how chemotherapy destroys large volumes of tumor cells is in terms of the cell-kill hypothesis which states that survival of animals bearing transplanted tumors is inversely related to the number of tumor cells remaining after treatment. The data upon which this theory was built were derived from the leukemia L1210 model system. In essence, it states that: (1) injection of a single cancer cell can ultimately lead to death; (2) the larger the number of cells in-
oculated into an animal, the shorter its survival; (3) the length of survival can be predicted based on the number of cells injected and the doubling time of the tumor population. Thus, with a growth fraction of essentially 100 percent and a doubling time of 12 hours, \(10^6\) cells will accumulate in 19 days following the injection of a single L1210 cell, 10 days after the injection of \(10^5\) cells, and five days after \(10^6\) cells. Skipper and his colleagues postulated, by extrapolating back to residual cell volume, that following a single drug treatment, an increase in the host’s lifespan of only two days represented a 90 percent cell kill, or a reduction of cell numbers from \(10^6\) to \(10^5\) (one log kill). A 99.999 percent reduction, an enormous figure, is equivalent to only a five log kill. Although survival is extended for 10 days, the disease cannot be cured unless the initial inoculum is \(10^6\) cells or less. To appreciate the full magnitude of the cancer problem, one must bear in mind that the average tumor nodule when first clinically detected certainly contains \(10^6\) cells. (Figure.)

Editor: Against such odds, how is it then possible to completely destroy a tumor population?

Dr. DeVita: Since a given dose of drug destroys a constant fraction of cells, not
a fixed number, it is necessary either to increase dosage within the limits tolerated by the host or to start treatment when the number of cells is small enough to allow tumor destruction at non-toxic doses. Unfortunately, the opportunity to treat small tumor volumes is uncommon in clinical oncology and the former alternative is the path often chosen. Toxicity to normal tissue from escalating doses of single agents has led us naturally to the use of drug combinations to achieve the same effect.

Editor:  

Does combination chemotherapy have any other advantage over single agent therapy?

Dr.DeVita:  

Yes. Whereas some single agents can produce lethal blockage of a single metabolic pathway, for example the inhibition of dihydrofolate reductase by methotrexate, combination regimens can be designed to attack multiple biosynthetic sites and/or inhibit several essential metabolic processes.

Editor:  

How would such blockage be accomplished?

Dr.DeVita:  

Sequential blockage involves the inhibition of enzymatic steps leading to the production of an essential metabolite. An example is the restriction of de novo purine nucleotide synthesis by the combination of azaserine and 6-mercaptopurine. Another approach is concurrent blockage, the simultaneous obstruction of parallel metabolic pathways involved in the synthesis of a common end product. The use of 6-thioguanine and arabinosyl cytosine which prevents the formation of a specific purine and pyrimidine respectively, as well as DNA polymerase, is representative. Finally, in complementary inhibition agents are selected to produce biochemical lesions at different loci in the synthesis of polymeric molecules. Alkylating agents which cross-link strands of DNA, in combination with antimetabolites which inhibit DNA synthesis and may prevent repair, serve as a possible example.

Although it is likely that the effectiveness of some drug combinations is related to blockade of essential metabolic steps, the design and use of combination chemotherapy remains, at present, an empirical process. When combinations have been designed solely on the basis of biochemical mechanisms without regard to clinical effectiveness, the results have been disappointing. In fact, some combinations carry the risk of interference, instead of additive or synergistic effects.

Editor:  

That's not completely clear to me.

Dr.DeVita:  

When two competitive inhibitors act on a single site, they compete for binding. Thus two equally potent agents would not be expected to enhance the effect of either alone. If one compound is less effective, antagonism will occur.

Editor:  

Does repeated exposure to chemicals lead to tumor resistance?
Dr. DeVita: Yes it can. Various mechanisms of drug resistance have been proposed based on studies of antibiotics; it may develop in an initially sensitive cell population through the stepwise induction of a resistant cell line, or it may be caused by regrowth of an inherently resistant population. If the latter mechanism exists in cancer cells, additional drugs may be required for each resistant cell line. The success of any chemotherapeutic program will therefore depend on the number of resistant lines in the tumor population and the number of available drugs which can be used in combination. This might account for the apparent success of many drug combinations in situations where single agents produced only temporary responses.

Editor: For what cancers has combination chemotherapy proven superior to single agent therapy?

Dr. DeVita: The treatment of acute lymphatic leukemia of childhood is a good example. The complete remission rate has improved from 22 percent with methotrexate alone to nearly 100 percent using two to four drugs in combination. At the National Cancer Institute, median survival in acute leukemia of childhood has improved from six months in 1956 when single agents were used (prednisone, methotrexate and 6-mercaptopurine) to 36 months in 1965 following the development of as many as eight active drugs and their use in combination. Unfortunately, no agent is capable of permanently reverting all leukemic bone marrow to normal. In a controlled trial, the overall remission rates for 6-mercaptopurine and methotrexate used alone were 48 percent and 29 percent respectively, while the combination produced a 59 percent response and, more importantly, twice the percentage of complete remissions than either of the single agents. Furthermore, duration of remission after single agent treatment, without maintenance, was short, averaging 45 to 60 days. In a randomized trial comparing 6-mercaptopurine to monthly vincristine and prednisone as remission maintenance treatment, the median duration of remission was 16 weeks for the single agent, compared to over 33 weeks for the combination.

Editor: Has the MOPP regimen also increased survival over single agent therapy for Hodgkin’s disease?

Dr. DeVita: Yes. Before the advent of combination chemotherapy in 1963, the complete remission rate was low in Hodgkin’s disease. Now drug combinations, particularly the MOPP program, can yield up to 80 percent complete responses. In addition, the duration of non-drug maintained remission has increased from 2.5 months for single agents to 36 months following MOPP therapy. Since the complete remission rate also rose from less than 20 percent to as high as 80 percent, these changes have, not surprisingly, been translated into longer survivals. In fact, the median survival for patients with advanced Hodgkin’s disease in the MOPP program at the National Cancer Institute will be in excess of nine years.
Editor: *Have any other solid tumors responded so dramatically to combination chemotherapy?*

Dr. DeVita: The most recent development is the use of drug combinations for carcinoma of the breast. The use of combination chemotherapy for breast cancer was heralded by the early reports of Greenspan, and more recently by Cooper, which showed that alkylating agents, methotrexate, 5-fluorouracil and the vinca alkaloids produced regressions in up to 80-90 percent of patients as compared to 20-30 percent using these drugs singly. Such results provided a stimulus for further studies. The so-called Cooper Regimen was employed in other hospitals; initial reports confirmed that combination chemotherapy could consistently produce higher response rates than single agent therapy. (Table.) However, the protracted use of vincristine and the almost continuous administration of cytotoxic drugs posed a potential limitation to such a regimen, especially as adjuvant chemotherapy in patients at high risk for relapse.

Editor: *How can this problem be circumvented?*

Dr. DeVita: The Medicine Branch of the National Cancer Institute has em-
ployed the cyclical administration of methotrexate (60 mg./m² [m² = BSA]) and 5-fluorouracil (700 mg./m²) on days one and eight with continuous daily oral prednisone (40 mg./m²) and cyclophosphamide (100 mg./m²) from day one through 14 (CMF-P). Therapy is then discontinued from day 14 to 28, and a new cycle of treatment is begun. This intermittent combination therapy was designed for ultimate use as adjuvant chemotherapy. The overall response rate in the first 25 patients treated was 64 percent with seven complete remissions. Although the median duration of response was eight months, the median survival of responders is more than 15 months compared to three months of nonresponders.

This regimen has been studied by the Eastern Cooperative Oncology Group in a randomized comparison with a single agent, phenylalanine mustard. The data show twice the response rate and double the duration of response for the combination group (52 percent and eight months) over the single agent (24 percent and four months); CMF was associated with four times the complete remission rate.

Editor:  

What is the next step?

Dr. DeVita:  
The next phase is to examine the role of combination chemotherapy as adjuvant treatment for patients at high risk of developing metastases. The results of the Scandinavian adjuvant trial have shown some advantage to adjuvant alkylating agent treatment in patients followed for more than three years. If the fractional kill of tumor cells is considerably better with combined treatment for patients with advanced disease, perhaps their adjuvant use in women with microscopically disseminated tumor at the time of mastectomy will result in a significantly greater number of disease-free survivors.

Editor:  

Thank you, Dr. DeVita.