www.nature.com/clinicalpractice/onc

Strong inference

Vincent T DeVita Jr

In November, Ferme *et al*.,[1] published an article on the treatment of early-stage Hodgkin's disease that said the following "Our study showed that a combination of chemotherapy and radiotherapy should now be the standard of care for all patients with localized stage, supradiaphragmatic Hodgkin's disease" and, added somewhat amazingly that "the remaining question now under investigation is whether early-stage Hodgkin's disease can be cured by chemotherapy alone".

In 1970, the cure of advanced Hodgkin's disease with combination chemotherapy was reported,[2] an observation that has been amply confirmed since then. The complete remissions in that study have remained durable over four decades. In the 1960s, Howard Skipper promulgated 'the inverse rule', which stated there is an invariable inverse relationship between the body burden of cancer cells and curability by chemotherapy in all experimental systems studied. In 1991, we published a randomized trial comparing MOPP chemotherapy with standard radiotherapy in poor prognosis early-stage Hodgkin's disease.[3,4] Even after 25 years' follow-up, chemotherapy won hands down when compared with radiotherapy alone, as it has in all studies since.[5] The collective response and survival data from the chemotherapy arm of our 1991 study and others like it that use standard and adequate chemotherapy suggest the inverse rule is operative in human systems. No one has shown a survival advantage of adding radiotherapy to chemotherapy for early-stage disease compared with standard and adequate chemotherapy alone. Despite this, very few large clinical trials have compared standard chemotherapy with combined modality regimens. This is important because we know that radiotherapy is associated with very substantial late carcinogenic effects, especially to the breast.

I use the phrase 'adequate chemotherapy' repeatedly because one has to question the quality of the chemotherapy administered in the Ferme study although no data are supplied in the paper to judge this. It is as if as long as the acronym is familiar, just stating that it was used is sufficient to assure the quality of administration. In the Ferme study, chemotherapy was administered in 92 different institutions and was capable of achieving a complete remission in only 64% of patients with early-stage disease, a substantially lower complete remission rate than is regularly achieved in patients with advanced disease who have a much higher tumor burden. When inadequate chemotherapy is used, radiotherapy always improves the outcome.

Strong inference and the inductive reasoning process have not been apparent in these large clinical studies of Hodgkin's disease

In 1964, John Platt coined the term 'strong inference' to describe a particular approach to research using an inductive reasoning process.[6] The process involves devising alternative hypotheses and designing experiments that will exclude a hypothesis. "How many of us," he said, "focus on experiments to exclude a hypothesis? We measure, we define, we compute, and we analyze but we do not exclude." If one examines rapidly moving fields you will find that inductive reasoning is the backbone of the design of experiments. In the laboratory, a hypothesis can be excluded in a week. Clinical investigators, because of the nature of their experimental subjects, have a special burden, but also a special responsibility, not to waste resources on experiments that take 5 years or more to complete but do not exclude a hypothesis.

Strong inference and the inductive reasoning process have not been apparent in these large clinical studies of Hodgkin's disease. The alternate hypothesis that standard and adequate chemotherapy alone would be equivalent to or better than combined modality therapy in early-stage Hodgkin's disease has not really been tested, let alone excluded. We already know we can cure it. I leave the reason for this to your imagination.

Supplementary information in the form of a reference list is available on the *Nature Clinical Practice Oncology* website.

VT DeVita Jr is the Editor-in-Chief of Nature Clinical Practice Oncology.

Competing interests
The author declared no competing interests.

www.nature.com/clinicalpractice
doi:10.1038/ncponc1094