Title
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Permalink
https://escholarship.org/uc/item/3cc110cg

Journal
The New England journal of medicine, 298(15)

ISSN
0028-4793

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Publication Date
1978-04-13

Peer reviewed
TERMINAL TRANSFERASE: ITS EVOLVING ROLE

Eventually, most patients with chronic myelocytic leukemia enter an aggressive phase of their illness, termed "blast crisis," that resembles acute leukemia except in its refractoriness to conventional chemotherapy. However, about 30 per cent of patients with leukemia in the blast-crisis phase achieve remission with rather simple chemotherapy: vincristine and prednisone. Considerable effort has been expended on defining the clinical, morphologic, cytochemical and cytogenetic characteristics of this subgroup of responsive patients. Lymphoblastic morphology and the finding of fewer than the normal diploid number of chromosomes are the two features most likely to be associated with response to vincristine and prednisone. However, these features do not invariably predict responsiveness.

Marks et al. in this issue of the Journal provide yet another (and perhaps more reliable) means of identifying the subpopulation of patients with chronic myelocytic leukemia in blast crisis who are likely to respond to vincristine and prednisone. The enzyme terminal deoxynucleotidyl transferase (TdT) is present in the white blood cells of approximately 30 per cent of such patients,1,2 and in contrast to original impressions, its presence does not appear to depend on the underlying morphology (lymphoblastic or myeloblastic). Sixty per cent of all patients (and 78 per cent of those under the age of 50) with TdT-positive cells in blast crisis responded to vincristine and prednisone whereas none of the patient with TdT-negative leukemia responded. This was a more reliable prediction of response than lymphoblastic or myeloblastic morphology. Unfortunately, this study leaves unanswered the question of whether TdT positivity was correlated with other objective laboratory tests such as cytochemical staining or chromosomal analysis, both of which are already available in many hospitals.

Despite the ability to predict hematologic response to vincristine and prednisone in this study, the median survival of responding patients (20 weeks) was only modestly better than that of patients who did not respond (12 weeks). The smallness of the benefit in survival may have been due to a wide variety of different treatment regimens employed after induction of remission by vincristine and prednisone. The authors suggest that the development of more effective consolidation and maintenance chemotherapy programs may improve the survival of patients with TdT-positive chronic myelocytic leukemia in blast crisis. An interesting corollary question is whether patients in whom TdT-positive blast crisis will develop can be identified early in their disease and whether chemotherapy with vincristine and prednisone can prevent overt blast crisis or improve survival of these patients. A few reports have already suggested that TdT activity is not present during the chronic phase of the disease. Another question raised by this study is why 40 per cent of TdT-positive cases fail to respond to vincristine and prednisone. It is interesting to speculate whether one of the two biochemical forms of TdT identified in normal thymus3 is only present in the responsive group and the other in the unresponsive group.

Why is there so much current interest in terminal transferase?4 This enzyme is a DNA polymerase that adds deoxyribonucleoside monophosphates to preformed DNA without a template.4 A survey of normal tissues in many species indicates that TdT is found only in cortical thymus and a subpopulation of bone-marrow lymphocytes.5 Recent studies suggest that TdT expression in bone marrow is regulated by thymic factors.6 However, its biologic role is unknown although it has been suggested that TdT may function as a somatic mutagen.7 An important consideration is the fact that it is not found in carcinomas or in non-neoplastic lymphoid states. At present, it can be regarded as a biochemical marker of lymphoid tissue (probably of early T-lymphocyte or null-cell origin).

In addition to being present in 30 per cent of cases of chronic myelocytic leukemia in blast crisis, TdT is found in 95 per cent of cases of untreated acute lymphoblastic leukemia,8,9 and these patients are usually sensitive to conventional chemotherapy including vincristine and prednisone. The enzyme level returns to normal with successful therapy and becomes detectable again with relapse of the disease. In contrast, the small group of patients with acute lymphoblastic leukemia without TdT-positive cells are resistant to conventional therapy. Two important clinical questions remain to be answered: does the emergence of resistance to conventional chemotherapy represent the disappearance of TdT-positive cells? Can early or late relapse be predicted from changes in the levels of TdT or in the distribution of TdT in subpopulations of bone-marrow cells?

TdT may also have a helpful role in the classification of some lymphomas.8 Only T-cell lymphoblastic lymphomas and some thymomas have high levels of TdT. Occasional cases of other diffuse lymphomas have elevated levels of this enzyme. In contrast, the known B-cell disorders like chronic lymphocytic leukemia and Burkitt's lymphoma are TdT negative. So
far, Hodgkin’s disease has also appeared to be TdT negative.

Terminal transferase has already proved to be of use in clarifying the classification of several types of hematologic cancers. The paper in this issue of the Journal now provides evidence that TdT is also a prognostic factor in influencing treatment of the blast crisis of chronic myelocytic leukemia. There is little doubt that further studies of this enzyme in acute leukemia, chronic myelocytic leukemia and lymphomas will have additional important implications for the practice of oncology.

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REFERENCES


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CREATIVE TENSION: FDA AND MEDICINE

Since joining the Food and Drug Administration, I have been exposed to a remarkable array of correspondence from well credentialed practicing physicians. Some of them are my former students from Stanford, others are former classmates at Harvard, and still others seem not to require any help from prior acquaintance. Many believe that the FDA is failing in its obligation to the medical profession in several ways: by appearing to ignore the wisdom of clinical experience in its decisions about drugs; by denying American physicians a number of new medicines readily available overseas and unduly delaying those developed domestically; and by regulating through edict rather than through education.

Let me begin by observing that a certain amount of tension between medicine and government regulatory activities seems unavoidable, appropriate and possibly even creative. I do not intend, by raising that prospect, to justify continuous hostility. But there are important respects in which the objectives of the two groups differ, and may even be in productive opposition.

We therefore should probably not expect, or even seek, to work in complete harmony, but surely we should do everything we can to avoid frank hostility, or outright misunderstanding. A first step in preventing such negative outcomes is a process that Lincoln called "disenthrallment."

For its part in the disenthralling process, I think the FDA has to liberate itself from the notion, with which it more than occasionally comforts itself and its medical constituency, that it regulates drugs and devices but not doctors. As much as we might wish otherwise, to regulate direct regulatory control over the way in which physicians and other health professionals work. But like other regulatory agencies, FDA has turned an important corner from policing the health-care system against fraud, quackery and bad manufacturing practices, to functioning as a regulator in the transfer of health technology. We have to be evaluated on the basis of how well we perform that function, and in a comprehensive way that counts loss of innovation as a cost.

For its part, American medicine must shed the view that regulation is something so fundamentally distasteful that it is best ignored. Let me hasten to say that negative conclusions about regulation do not bother me, if they are argued on the basis of a clear understanding of the process. But my communications from practitioners reveal, I think, a real deficit in the way in which medical education has dealt with the subject.

SHORTCOMINGS OF MEDICAL EDUCATION

My first point is that medical schools ignore the institutional aspects of health, and that the regulatory process is particularly neglected. For example, I can find only a few medical schools in which the pharmacology course includes an adequate examination of the process for the approval of new drugs. I think doctors ought to know much more than they do about adverse drug reactions, how to report them, and how to draw conclusions from the results, and that they should be much more familiar than they are with the basis for making risk-benefit assessments. The average physician in the United States will receive over $4,000 worth of direct drug advertising this year; it takes the drug industry less than a decade after graduation to surpass the public investment in the medical education of each doctor in the country. That is reason enough to make us want the nation’s medical schools to teach something of the social calculus of balancing drug efficacy and risk.