might make axillary node staging unnecessary.

In our report we used the first of these approaches because we could apply it to a very large data set (approximately 12,000 patients) without requiring clinical follow-up. In our predictive modeling efforts in patient sets for which we have detailed follow-up information, we are also examining the power of models for predicting relapse and survival that do and do not use information gained by axillary nodal staging.

Interest in this question is sparked both because, for some patients, the necessity of axillary dissection might be eliminated and because neoadjuvant programs confound the axillary nodal status, making it impossible to use this classical powerful prognostic variable for predictive modeling. Issues of selection, reproducibility, and standardization of prognostic factors to be used in these models and validation of the models should be an integral part of the modeling process regardless of the approach taken.

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Note

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Re: Reversal by Transferrin of Growth-Inhibitory Effect of Suramin on Hormone-Refractory Human Prostate Cancer Cells

Donat et al. (7) document a stimulatory effect of transferrin on the growth of three of five prostate cancer cell lines under specified culture conditions; they also demonstrate attenuation of the growth inhibitory effect of suramin by transferrin. A possible interpretation of the latter result is that transferrin acts by reducing the concentration of free (as distinct from protein-bound) suramin.

We (2) have shown that the impressive inhibitory activity of suramin on proliferation of neoplastic cells in vitro is attenuated by physiologic concentrations of albumin. This observation is consistent with the fact that suramin binds nonspecifically to many large proteins and also with the hypothesis that the growth-inhibitory activity (and toxicity) of protein-bound suramin is considerably less than that of free suramin (2). In most in vitro assay systems that demonstrate significant antiproliferative activity of suramin, subphysiologic concentrations of serum proteins are present, and thus the assays involve a higher concentration of free (compared with protein-bound) suramin than can be achieved clinically (2).

The impressive in vitro activity of suramin on HIV-1 (3) led to initial enthusiasm for this agent in the treatment of acquired immunodeficiency syndrome (AIDS), but subsequent clinical trials were disappointing (4). This discrepancy may also be related, at least in part, to attenuation of the actions of suramin by physiologic concentrations of albumin (5, 6).

A convincing demonstration of a specific reversal of suramin effect by transferrin that is unrelated to simple changes in free suramin concentration would have to include data showing that equimolar concentrations of other serum proteins lack the attenuating properties that Donat et al. demonstrate for transferrin.

While there is evidence for some clinical activity of suramin in prostate cancer (7), Donat et al. (7) discuss the fact that in vivo activity is less than would have been predicted on the basis of in vitro assays. It is likely that actions of suramin such as inhibition of CD4-gp120 binding, inhibition of binding of various peptide growth factors to their specific cell-surface receptors, and inhibition of neoplastic proliferation are progressively attenuated in the presence of increasing concentrations of any serum protein to which suramin binds. Efforts to increase in vivo efficacy of suramin by strategies to decrease binding of the drug to serum proteins unfortunately would be likely to increase toxicity.

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References


Response

Dr. Pollak correctly points out that the inhibitory action of suramin can be negated by binding to certain proteins such as serum albumin.

In this regard, Peehl et al. (7) examined the growth inhibitory activity of suramin on normal, benign prostatic hyperplasia, and prostate cancer cells. They found that albumin would antagonize suramin in a reversible way, but growth factors were unable to do so. This finding was important because they observed that these early-passage prostate cancers were less sensitive to the activity of suramin and that there was something being produced in the conditioned media of the tumors that would antagonize suramin in a reversible way. This factor was not identified. While we did not examine whether these prostastic lines were making transferrin, we were aware that the content of transferrin in the bone has been reported to be fairly...