Editorial

Doxorubicin-Polymer Conjugates: Further Demonstration of the Concept of Enhanced Permeability and Retention

Franco M. Muggia
Kaplan Comprehensive Cancer Center, and New York University School of Medicine, New York, New York 10016

Clinicians have not thought enough about drug distribution. Whereas in most fields, drug efficacy is unlikely to be highly dependent on targeting, in cancer therapeutics, targeting is becoming increasingly important, not only for the “warheads” directed specifically to tumors, but also for our already established antineoplastic drugs. The importance of such targeting has only recently been recognized by clinicians, largely because of the widespread attention that tumor angiogenesis and antiangiogenic strategies have received (1). Actually, the concepts behind EPR by tumors were articulated more than a decade ago (2, 3). The article by Vasey et al. (4) in this issue of Clinical Cancer Research constitutes “proof of concept” using a doxorubicin-polymer complex to achieve EPR.

The essential hypothesis behind the EPR concept is the differential localization of macromolecules as well as small particles in the tumor microenvironment vis-à-vis the microenvironment in normal tissues (3). Passive accumulation of a drug-polymer conjugate or drug-containing liposome within a tumor is probably a reflection of a hyperpermeable vasculature. Other factors, such as poor lymphatic drainage, are also likely to play a role. The subsequent steps leading to internalization and/or drug release probably vary among the agents used and may also vary among tumor types. However, recent work by Duncan and Sat (3) in s.c. B16 and L1210 murine tumors suggests that tumor size, but not tumor type or macromolecular form, determines the percentage of localization of the administered dose.

The Phase I and pharmacokinetic study by Vasey et al. (4) is an even more impressive demonstration of how this concept of localization alters the tolerance of doxorubicin. Doxorubicin has been a favorite target for developing strategies directed at changing its therapeutic index. Not only has its activity against various solid tumors been an attractive feature, but many studies have pursued its mechanisms of action and differential effects on the heart versus other tissues and tumors. Improvements in the therapeutic index of doxorubicin from liposomal encapsulation were summarized almost two decades ago (5). Doxorubicin has also been linked to monoclonal antibodies; such conjugates had impressive activity against animal tumors (6), but clinical experience remains unpublished. The drug has also been given by the intra-arterial route and in conditions of hepatic perfusion followed by extracorporeal filtration. Except for the liposomal preparations that found their way into the treatment of Kaposi’s sarcoma (7), a tumor characterized by very abnormal vasculature and anthracycline sensitivity, other methods of increasing the therapeutic index of anthracyclines are still under investigation.

The unique aspects of the current study lie not only in the drug-polymer conjugate, but also in the “dramatic increase in administered doxorubicin equivalence” that was tolerated, coupled with the intriguing possibility that this drug complex has activity against doxorubicin-refractory tumors such as colorectal cancer and non-small cell lung cancer.

Another aspect that the authors emphasize is the versatility of the copolymer conjugate system and the possibility that specific localization may be achievable through the introduction of certain sugars such as galactose in the polymer structure to target the hepatocyte glycoprotein receptor. In addition, other drugs may possess advantages over doxorubicin, and conjugates are already being prepared with the potent methoxymorpholino-doxorubicin, paclitaxel, and platinum. The study by Vasey et al. is clearly only the first lesson being taught to clinicians about this drug-polymer complex family. Liposomes are undergoing a similar evolution from classical liposomes to long-circulating pegylated liposomes (enhancing its tumor localization) and immunoliposomes containing anti Her2/neu (enhancing tumor uptake; Ref. 8) and, finally, the testing of other drugs such as platinum in liposomes (9).

Whether PK1 ever becomes a clinically useful drug or not, the study should acquaint clinicians with important pharmacological concepts that we are just beginning to appreciate. The ability to determine drug localization in tumors has been steadily improving, and noninvasive means promise to allow us to do this better during the development of a drug. This study represents one example of how this question is beginning to be addressed. For a generation of oncologists familiar with the toxicities of doxorubicin, the attenuated effects of the drug-polymer are quite a remarkable achievement, even if many questions remain as to ultimate efficacy and tolerance on repeated administration, which is currently still quite preliminary.

References
