Editorial comments

Both topical and systemic chemotherapy contribute significantly to the current management of recurrent superficial and advanced bladder cancer, respectively. However, clinical results have not lived up to initial expectations, and innovative approaches to improve the therapeutic index are required.

One such approach is the investigation of how bladder cancer cells develop resistance against the chemotherapeutic agents commonly used in clinical practice. In addition, methods are required to reverse, circumvent, or surmount drug resistance, thereby possibly increasing the number of cancers that can be cured. The paper by Seemann et al. provides a progress report on the establishment of a further cell culture model to investigate MDR in bladder cancer – it is a progress report in that it raises more questions than it answers.

Continuous exposure of a human bladder carcinoma cell line to doxorubicin resulted in doxorubicin resistance, with cross-resistance to another anthracycline and to vinblastine. Adding a functional test such as rhodamine 123 efflux combined with immunohistochemical semiquantitation of P-GP expression clearly points to *MDR1*, the "classic" mechanism underlying MDR, as a contributor to the resistance profile observed in this particular cell line. However, immunostaining (in arbitrary units) only rises from 2 to 8, whereas the level of resistance increases 96-, 132- and 168-fold (depending on the drug), and R-verapamil chemosensitization does not fully restore sensitivity to the anthracyclines. Hence, alternative mechanisms of MDR come to mind, and the elucidation of resistance factors such as MRP, GST, Topo I and II will be imperative for future studies on this model.

Similarly, the data on mitomycin C need putting into context with additional information on the resistance pattern against a panel of natural product substances thought to be recognized and expelled by P-GP. Significant abberations would then have to be subjected to molecular analysis to pinpoint possible mutations in P-GP (or other factors). Again, to avoid conflicting results due to the heterogeneity of subpopulations, cell line RT112/D21 awaits cloning, which will be indispensable for a more profound characterization. Clinically, several publications (of which two have been cited: refs. [17, 25]) have reported the introduction of verapamil as an MDR modulator in conjunction with anthracycline therapy/prophylaxis.

Both these studies as well as a more recent report [1] have described a negative result by failing to reduce the recurrence rate with the combination of a chemosensitizer and a chemotherapeutic agent. In another study [2], a marker lesion of superficial bladder cancer was used to evaluate the therapeutic efficacy of a doxorubicin/verapamil combination. Some remissions were documented, but the non-randomized study design should prevent us from drawing further conclusions.

Clearly, much more work is needed to define a potential role of MDR in the management of patients with bladder cancer. The tools are now available (in terms of MDR-bladder cancer models); the promise is yet to come.

References

1. Park J, Shinohara N, Liebert M, Noto L, Flint A, Grossman HB (1994) P-Glycoprotein expression in bladder cancer. J Urol 151:43
2. Naito S, Kimiya K, Ueda T, Kumazawa J, Omoto T, Osada Y, Iguchi A, Ariyoshi A, Sagiyama K (1992) Intravesical therapy with Adriamycin plus verapamil and patients with superficial bladder cancer: a pilot study. Urol Int 48:270