Expert’s comments:
Ways to improve patient survival from bladder cancer include: prevention; earlier diagnosis; better staging; more effective systemic therapy for advanced disease. However, stage and grade can take us only so far. Moreover, given current diagnosis and limitations in staging, invasive bladder cancer all too often is a systemic disease. While excellent radical surgery, including extended lymphadenectomy, is a cornerstone of treatment, more is required for optimal results in many patients.

Alterations in key molecular markers confer heterogeneous risk in a given tumor of a given grade and stage. A major limitation in clinical trials of neoadjuvant or adjuvant chemotherapy for patients with bladder cancer has been the failure to account for these differences. Karam et al showed that alterations of four apoptotic markers individually, and in combinations, were independent and cumulative risk factors for disease recurrence and disease-specific mortality. The obvious implication is to consider patients at higher risk by “molecular staging” profiles for neoadjuvant or adjuvant chemotherapy trials, or for more frequent follow-up. The same investigators have published similar findings for alterations of the four cell cycle regulators, p53, p21, p27, and pRB, in patients with bladder cancer [1]. Many teams of investigators around the world are taking a similar approach and the list of potential molecular pathways and targets is long. Finite patient numbers and resources require a coordinated approach to the study and implementation of such findings into clinical practice. Alterations of the four apoptotic markers in the study by Karam and colleagues may or may not turn out to be the most useful in the treatment of patients with bladder cancer. However, this approach has enormous potential for improving care for patients with bladder cancer.

Reference

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Re: Limited Tissue Penetration of Taxanes: A Mechanism for Resistance in Solid Tumors
Kyle AH, Huxham LA, Yeoman DM, Minchinton AI

Expert’s summary:
Limited drug penetration in solid carcinomas is a potential cause of resistance to anticancer drugs. Taxanes, such as docetaxel and paclitaxel, are currently undergoing a new phase of development. To improve the understanding about their ability to penetrate and distribute relative to blood vessels within solid tumors, tissue penetration of docetaxel and paclitaxel was studied in an HCT-116 tumor xenograft, a multilayered cell culture (MCC), and a three-dimensional cell culture model. The authors observed limited penetration of both taxanes, with only a little drug reaching further than 100 μm into the tissue. Interestingly, paclitaxel revealed a 2-fold greater penetration than docetaxel. In the tumor xenograft model, reduced drug exposure to cells far from vasculature is one of the various factors influencing response to drug treatment. The study observed a reduction of 75% in S-phase cells in cells nearest to vessels compared to a 50% reduction in tissue 150 μm away. In the MCC-based data, a 10-fold increase in reservoir docetaxel concentration was required to initiate a response in cells 150 μm into the tissue equivalent to the response seen in cells directly exposed to the drug. The author concluded that their results indicate an important mechanism of tumor resistance to taxanes.

Expert’s comment:
Prostate cancer remains to be the leading cause of cancer-related death in Western Europe, with a chance of dying due to prostate cancer of 1:30. Multiple theories for the development of androgen-independent prostate cancer exist, but the one true mechanism has not been described today [1]. Since the introduction of docetaxel-based chemotherapy in 2004, the treatment of androgen-independent prostate cancer has been revolutionized [2,3]. Even though the survival benefit in these studies was statistically significant, it was only about 3 mo considering all the potential drawbacks in the study design. Nevertheless, docetaxel-based chemotherapy has been set as the new standard of care in these patients. However, the response rate, defined as a reduction of prostate-
specific antigen of 50%, was only 45–50% [2,3]. Furthermore, after several years of experience using docetaxel-based chemotherapy in prostate cancer, we have learned to deal with the possible side effects this therapy.

Experts are still discussing the optimal timing to start chemotherapy. A current study investigates its role as adjuvant therapy following radical prostatectomy in high-risk prostate cancer cases. Due to the known grade migration (the so-called Will Rogers phenomenon), this approach may become even more important. New chemotherapeutic drugs are currently being investigated in men with docetaxel-resistant and androgen-independent prostate cancer.

The study by Kyle et al is extremely important to improve the understanding of tissue penetration of new taxane derivates [4]. Using the effect-based MCC assay, one may be able to screen compounds aimed at reaching and killing cancer cells far away from blood vessels for tissue penetration capabilities [4]. A poorly penetrating drug will require a higher systemic concentration, leading to an increased systemic toxicity. Thus, by improving a drug’s capability to penetrate into the tissue one may be able to decrease the concentration, which may lead to decreased toxicity. Furthermore, improved drug penetration may increase the window of exposure of cancer cells to therapeutic drug levels.

In the emerging field of multimodal treatment planning and novel therapeutic treatments based on individual risk stratification, newly developed compounds with improved ability to kill cancer cells are mandatory. Tissue penetration of drugs is one of the possible ways to achieve this goal and it will be interesting to observe the advances being made in the near future.

References


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