Tests to Detect Drug Resistance in Malignant Tumors. Should They Guide the Clinician's Choice of Treatment?

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Resistance to cytostatic drug treatment is an all too well known phenomenon to a physician treating cancer patients. A wealth of information on multiple drug resistance (MDR) has been emerging over the past 15 years. We certainly have learned a lot about drug resistance mechanisms. Various complex systems seem to be involved, such as transmembrane transporter genes and proteins (MDR1 gene and p-glycoprotein), DNA repair mechanisms (topoisomerase II gene and its product) or cell detoxification processes related to glutathione and glutathione-S transferase with its many isoenzymes. Several reviews have covered this topic recently [1-4]. These MDR mechanisms are not unique to cancer but have also been observed in the treatment of infectious microorganisms.

The paper by Volm and Mattern [5] in this issue compares two ways to test for drug resistance in non-small-cell lung cancer (NSCLC). On the one hand, there is a global test that detects drug resistance in vitro. On the other hand, tests are performed that measure the individual resistance mechanisms having been found to be associated with drug resistance. The authors find a good correlation between the in vitro short-term test and 4 out of the 6 individual parameters that were analyzed immunohistochemically. The reader may infer from these findings that clinical tumor response may be correlated to the results of an in vitro test or to results from immunohistochemical or molecular findings. So he may ask, 'Are there currently tests available that tell me which patients do I have to treat or even which patient can profit from which drug?' The best global test for drug resistance is certainly the assessment of tumor response in a patient given chemotherapy for his cancer. There is a variety of promising in vitro tests that may predict for tumor response such as the DiSC test [6], the MT assay [7] or the assay described by Volm and Mattern. However, the clinical relevance of these tests is still debated and none of them has found its way into routine daily use. They may identify which tumor will respond to treatment, but they do not offer a satisfactory therapeutic alternative and herewith become prognostic factors similar to axillary node status in breast carcinoma or an elevated lactate dehydrogenase in the non-Hodgkin's lymphomas, and everyone of us has seen enough of these risk factors lately.

However, if we plan chemotherapy trials in NSCLC, we should implement such tests and then we could give an answer to the question whether it may be worthwhile to treat just the group with a specific pattern of in vitro sensitivity. But until now no such data is available and none of us would exclude a patient from treatment solely on the basis of the available global resistance tests.

How about the various assays that test for changes of the individual drug resistance systems mentioned above? Although the discussion of technical aspects would go too far, we have to be aware of the fact that a multitude of pathophysiological aspects can be measured, starting from alterations of gene regulation, the gene itself, its message, protein expression, phosphorylation and, finally, the function and activity of a certain protein. So the measurement of, for example, the amount of protein present may just tell a part of the whole story. If these parameters are found in a tumor not having been exposed to cytostatic drugs then it may just be a hypothesis that proteins like the MDR1 product p-glycoprotein (p-gp) have anything to do with intrinsic drug resistance.

This hypothesis has beautifully been tested in leukemias, lymphomas and multiple myelomas where clinical trials with MDR-modifying agents have demonstrated that drug resistance was correlated with the emergence of p-gp in tumor cells and that tumors which have become resistant to chemotherapy again became sensitive if the same chemotherapy was given with the addition of MDR modifiers [8-10]. So this would confirm that the emergence of p-gp during chemotherapy is not just a new risk factor but is clinically relevant and even 'treatable'. But still the data are too controversial to already advise colleagues to determine these parameters on a routine basis. The determination of p-gp is probably close to routine use in leukemias and myelomas, but measurements

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such as topoisomerase II, thymidilate synthase or metallothionein levels need to be evaluated further before they can be introduced into the clinic.

What about the impact of such resistance parameters at initial diagnosis of a tumor, at a time when no chemotherapy has been given which could have selected for clones expressing, for example, p-gp or an elevated GST pi? Again, from Volm and Mattern's work we could conclude that the measurement of these parameters may be clinically relevant. However, the basic problem remains in the case of NSCLC that we do not have substances that are potent enough to treat lung cancer. Cytostatic treatment so far has had little impact on the outcome of NSCLC because the currently available drugs are unable to satisfactorily eradicate the tumor cells. Still it seems that drug sensitivity in NSCLC may be related to p-gp and other resistance parameters. Therefore the question comes up whether MDR modifiers given together with initial chemotherapy may render these tumors more drug-sensitive. Unfortunately, until now there are no data showing that an intrinsically resistant tumor which, for example, is p-gp-positive responds to chemotherapy if it is given together with an MDR modifier. Why is that so? There is probably a multitude of other resistance-related systems whose function we currently do not know. A system such as MDR1/p-gp may have a significant impact on one tumor type whereas it may just be an epiphenomenon in another one.

Many resistance systems probably act together and, therefore, their impact can only be quantified if they are individually measured and put in relation to each other. We still seem to be at the beginning of understanding drug resistance. We have discovered some pieces of the puzzle that may be clinically relevant in a fraction of the tumors we know. It is our opinion that at this time it is too early to use any of these global tests or determinations of individual MDR mechanisms as a routine analysis. The evaluation of such factors should be implemented into clinical trials so that we can learn more about the basic pathophysiology of the resistance phenomenon. This task can only be accomplished if clinicians, pathologists and molecular biologists further intensify their close collaboration.

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