Therapeutic Failure and Drug Resistance

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Prof. Dr. med. R. Osieka, Medizinische Klinik IV der RWTH Aachen, Pauwelsstraße 30, D-52074 Aachen (Germany)

Dear Prof. Heimann, dear colleagues from the technical university, speakers, guests and participants! It is a great pleasure to welcome you to the Third International Meeting on Drug Resistance here in Aachen. This meeting is also the 10th anniversary of all meetings exclusively devoted to this subject in Germany.

In 1983, the first meeting was convened in Regensburg under the leadership of Profs. Schönenberger, Seeber and myself. A wide variety of subjects was covered, ranging from the development of new and less toxic nitrosourea and platinum derivatives to completely new compounds, such as ether lipids. Physical treatment modalities such as hyperthermia and radiation sensitizers were explored. Dr. Bridget Hill was the first to show that the relationship between ionizing irradiation and drug resistance was not one of complete innocence. Dr. Schimke demonstrated the role of methotrexate-resistant gene amplification. Drs. Dano and Skovsgaard manifested altered resistance by a change in the accumulation of multidrug-resistant drugs. Dr. Len Erickson quantitated nitrosourea-induced damage to the genome at the macromolecular level using the alkaline elution technique and applied it to monitor impaired DNA repair.

Five years later at the next meeting in Munich P-glycoprotein (PgP) was elegantly demonstrated to be the cause of multidrug resistance by Dr. Victor Ling. During that meeting, I became acquainted with Dr. Manfred Dietel's work on how membranes manage to avoid potential drug damage by export mechanisms other than PgP.

Cytokines to stimulate myelopoiesis were already at hand and certainly raised hopes to overcome dose-limiting myelosuppression in conjunction with dose-intensifying strategies. In 1990, here at Aachen University the issue was narrowed down to modification of drug resistance. Since it was by then well known that mechanisms of drug resistance were not exclusively expressed in neoplastic cells, the term modification rather than reversal of drug resistance was felt to be more appropriate.

The theme of new drug targets received an additional twist by the information on the role of topoisomerase II in multidrug resistance presented by Dr. Beck. His lecture and subsequent publications have had an ongoing impact on grant applications and published research not only in adult but even more so in pediatric oncology in Germany. In my opinion, such developments beautifully emphasize the scientific and educational importance of meetings on drug resistance. Very late in the preparative stages of the meeting I had asked Dr. Kevin Scanlon to present his findings on the interaction of cyclosporin and cisplatin. His data on altered gene expression by cyclosporin introduced a new point of view on responses to chemotherapy at the transcriptional level. In 1991, the meeting in Kiel gained scientific momentum and attendance. Among many other new data, highly specific treatment with ribozymes to neutralize the effects of altered

oncogenes were introduced by Dr. Scanlon. Subsequently, many investigators were able to demonstrate excellent in vitro modification of P-gp-mediated drug resistance, but the design of clinical trials still remains an intriguing problem.

During the preparations for the present meeting I came to recognize that some aspects of the resistance issue were to change fundamentally in the near future.

The hitherto serendipitous road to drug resistance step-by-step selection procedures already revealed a fairly large number of interesting mechanisms by which resistance might be conferred to tumor cells. A much wider approach to uncover such mechanisms has been pursued by Dr. Roninson, who together with Dr. Beck introduced the concept of genetic suppressor elements. Today, an oncologist may be faced with a cosmos of interesting mechanisms of drug resistance but still does not know how to apply this information to the decision making process, in actual treatment. Therefore, standards in evaluating drug resistance similar to those known in blood chemistry need to be established before knowledge on drug

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resistance becomes a reliable part of clinical treatment protocols. This should include ratings on the availability, reliability and combinatorial use of various assays.

Strategies directed at the evolution of drug resistance so far have strongly relied on tumor cell eradication by intensive combination chemotherapy or modification of resistance. Other innovative methods are badly needed.

The concept of DNA as a target for alkylating agents and, for example, ionizing irradiation has withstood the test of time. Nonetheless it is only through analysis of gene-specific damage rather than global indicators of macromolecular DNA damage that the question as to why some tumors respond better than others to chemotherapy might be resolved.

In contrast to established principles of general pharmacology, antineoplastic chemotherapy has been said to lack specific targets. This, however has changed dramatically with the discovery of gene alterations unique to cancer cells. Success may still be elusive since in situ availability of highly specific binding drugs remains too low and/or the knock out of the target is in some way compensated by regulatory mechanisms.

The definition of drug resistance has gained immensely from analogies to antimicrobial testing starting with cell cloning experiments performed by Theodore Puck and taken further by Drs. Hamburger and Salmon, for example.

Other principles, such as the induction of differentiation and/or programmed cell death, may well completely rewrite the story of drug resistance and therapeutic failure. Induction of apoptosis may form the key element of therapeutic success for some tumor entities as we will hear from Dr. Debatin from Prof. Krammer's group in Heidelberg.

(7) The use of retinoic acid in promyelocytic leukemia is a milestone in modern leukemia treatment. Therefore, the rationale behind its use, as discovered by Dr. Christine Chomienne, explaining modes how patients become resistant to retinoic acid treatment had to be included in our meeting.

In an era where the clamor over dwindling resources has captured headlines health policy will have to be restructured also.

We wish to express our gratitude to the many drug companies which still believe in the rational development and use of antineoplastic agents. Their support was crucial to the success of this meeting and the availability of international expertise. To the best of our knowledge, the results

on drug resistance will foster the development of new agents, decrease toxicity by either structural modification or by selective detoxification and make better use of existing agents in well-guided dose intensification protocols.

Ceilings imposed on health expenditures in conjunction with the principle of a patient's right to self-determination and the blurring by science of the hitherto well-defined boundaries between life and death present complex problems in medical decision making. Rational drug therapy seems to offer a solution to these problems. At the same time as we reach out for new dimensions in understanding mechanisms of drug resistance we must not lose the public and private openness to the cause of rational drug treatment.

Tremendous progress has been made during the last 10 years in the research on drug resistance. Furthermore, (1) microscopic subclassification of tumors, (2) imaging techniques and (3) monitoring disease by tumor markers have been improved, too.

Major advances in medical oncology, however, have also been made in other fields. Adjuvant treatment of colorectal cancer probably saves more lives than all dose intensification protocols taken together. Salvage treatment protocols mainly rely on the principle of dose intensification in general and not on the detection of resistance mechanisms. So far maintenance therapy in acute leukemia with its repetitive drug exposures seems to contradict some observations on the evolution of drug resistance. My attempt to highlight some of the achievements contributed by our present panel of speakers is certainly flawed with some errors and ignorance.

Despite the new horizons opening up to clarify the potential of both normal and malignant cells to beat the attack by many antineoplastic agents it may be premature to expect immediate results in medical decision making. Basic science should not derive its support from immediate or short-term goals. Sharing new information on drug resistance and deducing the ensuing hypotheses which merit clinical testing will remain a formidable task for the future.