# Symposia

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## CIRCUMVENTION OF CHEMO-RESISTANCE: AN OVERVIEW

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Rational circumvention of chemo-resistance in cancer requires knowledge of the underlying mechanisms and this is currently not available. Nevertheless, a number of approaches have been pursued, and this illustrates the frustrations felt by clinicians treating a range of tumour types. In this symposium several avenues will be explored.

Multi-drug resistance, mediated by P-glycoprotein, is a laboratory observation of uncertain clinical relevance; however, its reversal can easily be achieved experimentally and a number of clinical trials have been pursued. To date a key feature has been the important pharmacokinetics interaction between the modulating agent and the cytotoxic drug under study. Multidrug resistance (MDR) may be mediated by other cellular means, which may be amenable to alternative modulators; these may also be effective for agents other than those classically involved in MDR.

Factors which could underly resistance to other important drugs, e.g. cisplatin, include defective drug transport, enhanced drug inactivation and increased DNA repair. Potential means for modulation for each of these include the development of platinum analogues, intracellular glutathione depletion, and the use of repair inhibitors; to date their clinical value is unclear. A key determinant for resistance to many agents, including cisplatin, could be the failure of tumour cells to engage the process of apoptosis. As the genetic controls for this process are increasingly being understood, the possibility exists for rational new means for resistance circumvention, provided that the clinical relevance of this pathway is confirmed.

As well as 'cellular' factors, chemoresistance can be due to 'pharmacological' factors, which include considerations of dose and schedule. This may be particularly relevant for antimetabolites, such as 5-fluorouracil and cytosine arabinoside, whose activity does seem to be schedule-dependent. However, modulation of chemo-resistance based on the single manoeuvre of increasing dose has not yet made a major impact in solid tumors, and it is possible that the most successful strategy will be to employ a number of modulation techniques.

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## CIRCUMVENTION OF MULTIDRUG RESISTANCE

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Two members of the superfamily of ABC transport proteins, Mr 170.000 PGP and Mr 190.000 MRP, have been identified as multidrug resistance genes. Both genes can act as cellular efflux pumps for natural product anticancer drugs, like anthracyclines, Vinca alkaloids, and epipodophyllotoxins. Pgp and MRP are expressed in a variety of tumours, including haematological malignancies. Pharmacological intervention by competitive inhibition of PGP and MRP has been studied *in vitro*, and clinical studies have been performed with the aim to circumvent (primarily PGP-mediated) MDR. In summary, these attempts have not been very successful, so far, in solid tumours (e.g. kidney and colon cancer) with de novo expression of PGP. For haematological malignancies the results obtained encouraged randomized phase III trials (which are ongoing). The effects of the so-called reversal agents on clinical tumour responses seen in pilot studies, are likely due to specific inhibition of PGP in tumour cells and to altered pharmacokinetics of the cytotoxic drugs. The general idea is that more effective and less toxic reversal agents are needed for clinical trials. However, mdr-knockout mice appeared to be extremely sensitive for xenobiotics. Thus, upon clinical use of highly effective, second generation reversal agents, altered (life-threatening) toxicity profiles should be anticipated.

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## CIRCUMVENTION OF MDR: ALTERNATIVES TO THE AFFLUX PUMP

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Various genes responsible for multidrug resistance have been characterized. Factors involved are overexpression of the P-glycoprotein (P-gp) pump, an overexpression of the multidrug resistance related protein (MRP), altered topoisomerase II enzyme and increased detoxification of the drug. With (RT)-PCR, Northern and Western blotting, immunohistochemistry, and functional assays it is possible to detect the presence of the factors in human tumors. The exact role of each of these factors in the tumors of patients is unknown. Within a human tumor more than one factor plays a role and within a tumor there can be regional differences. Modulation in the clinic is performed with P-gp blockers such as verapamil. It is unknown whether the drugs for e.g. P-gp blocking do reach an effective tumor concentration and do indeed block the pump in patient's tumors. Currently, clinical studies with functional detection methods to localize MDR pumps are ongoing with e.g. $^{99m}$Tc-Sestamibi. For the MRP pump, which was found to be the glutathione-conjugate pump, no modulators are available. Therefore, insight in glutathione metabolism may be of increasing value. Topoisomerase II, drug target for a number of drug measurements, may be another options to rationalize chemotherapy treatment. It is increasingly realized that modulation of more than one MDR mechanism is required in the clinic.

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## PLATINUM RESISTANCE AS PARADIGM OF PRECLINICAL AND CLINICAL CONCEPTUAL DIFFERENCES

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Resistance to anticancer agents is the subject of intensive basic and applied research. Its definition is quantitative and expressed as n times the concentration of the agent in question, mostly *in vitro*. Schedule dependency, and concentration × time effects are seldom studied. No standards of normal sensitivity exist, since in most cases the resistance level is gauged against the parental line, seldom of human cancer origin. The medical oncologist perception of the resistance phenomenon is relative to both the quantitative aspects of antitumor response evaluation and qualitative respect to dynamics tumor progression. Clinical resistance definition is adhoc for every tumor type, and undergoes continuous evolution with new drugs and putative manipulations for its circumvention (modulation, dose, schedule). Resistance to platinum compounds has been studied through basic research and the main mechanisms have been elucidated. Only recently the relevance of the different mechanisms is being correlated to disease and natural history specific clinical settings. Non cross resistance between distinct platinum compound families has been perceived for over two decades, but its clinical potential was never implemented. Dose response and dose intensity delivery issues are also a long standing subject in Platinum efficacy assessment. The association of Cisplatin and Carboplatin, dose intensive schedules (weekly administration), the interaction with other agents, and the availability of Oxaliplatin, a non cross resistant DACH compound offer tools for the medical oncologist that will expand further the therapeutic role of Platinum compounds. Applied research preparing a solid rational for this horizon should be adapted to clinically relevant targets.

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## CIRCUMVENTION OF RESISTANCE TO 5-FLUOROURACIL BY SCHEDULE-ORIENTED BIOCHEMICAL MODULATION IN ADVANCED COLON CANCER PATIENTS

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We have recently demonstrated that bolus FUra treatments of human colon carcinoma cells, HCT-8, produce resistance via an RNA-related mechanism, while prolonged exposures to the fluoropyrimidine is responsible for a DNA-related mechanism of resistance. In addition, cells

resistant to short term FUra exposure retain full sensitivity to the continuous exposure to the same agent. These data suggest that biochemical modulation of FUra should take into account the schedule of fluoropyrimidine administration. Based on this rationale, we completed a phase 2 trial of schedule-oriented biochemical modulation of FUra in advanced colorectal cancer patients, based upon a hybrid regimen of 2 biweekly cycles of FUra bolus (600 mg/sqm), preceeded by (24 h interval) MTX, 200 mg/sqm (in order to maximize the RNA effect of the drug) alternating with FUra continuous infusion, 200 mg/sqm daily for 3 weeks, modulated by leucovorin, 20 mg/sqm weekly bolus (in order to maximize the DNA effect). Among the 33 consecutive patients accrued there were 3 CR and 13 PR (RR = 48%, 95% CL, 31–66%). Eleven patients had a minor response and 4 of them showed tumor shrinkage ranging between 46% and 49%. After a median follow-up time of 26 months, 10 patients are still alive. The median PFS and overall S were 9.6 and 20.2 months, respectively. The low toxicity of the bolus part of our regimen prompted us to pursue its intensification by adding a further modulator to MTX. Our recent finding of a strong synergism between bolus FUra and IFN, obtained *in vitro* on the same tumor model, generated a phase 2 trial employing the same regimen plus IFN (3,000,000 U im q12h × 4, starting at the time of FUra bolus administration). Among 42 patients 4 CR, 15 PR (RR = 45%), 6 MR and 10 SD were obtained. Since the results of the two trials are similar showing twice as much activity and less toxicity than bolus FUra +LV or MTX → FUra, a randomized comparison is now ongoing between our original hybrid regimen without IFN and MTX → FUra.

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## COMPARISON OF CANCER PATIENTS SURVIVAL ACROSS EUROPE

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The EUROCARE study group was funded by the European Union to assess the survival of cancer patients throughout Europe. The first data analyzed and published in collaboration with the International Agency for Research on Cancer show variations between countries in survival probability for colo-rectal, stomach and breast cancer for which stage at diagnosis is an important determinant of survival. In contrast, little difference is seen for cancers which respond well to cytotoxic therapy such as Hodgkin's disease or testicular cancer. It is suggested that variations in the speed of access to the most adequate care system may explain part of the observed differences.

The steering committee of the group consists of F. Berrino, J.W. Coebergh, M. Coleman, J. Estève, J. Faivre, T. Hakulinen, C. Martinez, M. Sant, A. Verdecchia, S. Welson.

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## IMPACT OF QUALITY CONTROL ON TREATMENT OUTCOME

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Quality control in radiotherapy reinforces the quality established within the framework of general programs of quality assurance.

The control applies to the most critical aspects of treatment, thus enabling the elimination of systematic and sometimes random errors.

Can quality control have an impact on treatment outcome?

In radiotherapy, the result is dependent on several factors, starting with the exactitude of the initial diagnosis and ending with the therapeutic follow-up. In the literature, data show that some loco-regional failure and, in certain cases, the decrease in survival can be attributed to treatment error. Quality control in radiotherapy enables the analysis of various typical errors and their consequence, particularly with regard to target volumes, irradiation fields, dose, or errors in calculation. This knowledge can limit errors to a minimum. Various systems, more or less sophisticated, should be able to limit errors before or during the treatment. Quality control leads to the improvement of treatment outcome; some examples will be given. However, these results are not always obvious. Quality control has a role to play in certain clinical circumstances which are difficult to analyze without precise and objective information on patient outcome. It can be an important component in the treatment of localizations that have had mediocre results.

Besides its contribution to the improvement of local control and survival, quality control can also be an essential means of improving and decreasing post-therapeutic complications.

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## THE IMPACT OF CANCER NURSING ON TREATMENT OUTCOMES

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The care of patients with cancer, from diagnosis to terminal care, demands the support of a multidisciplinary team in both hospital and community settings. Nurses spend more time caring for this group of patients than do any of their clinical colleagues. Therefore nurses are ideally placed to play a pivotal role in the co-ordination of the diversity of care which is required for the patient with cancer. It has been demonstrated that intervention by clinical nurse specialists enhances patient care and results in cost reduction in a number of areas and that nurses are critical to the success of clinical trials. Currently treatment outcomes are measured both in terms of survival and quality of life of the individuals concerned. In each of these areas nurses have a significant role to play through clinical practice, education and research. Advances in these areas will ensure the continued improvement in the provision of nursing care and hence the efficacy of treatment for patients with cancer.

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## WHY IS CANCER OUTCOME DIFFERENT?

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The first evidence that patients treated in a research protocol fared better than the rest came from Stiller's analysis of children with cancer. He compared the outcome of those treated in Medical Research Council (U.K.) trials with those treated in peripheral non-academic paediatric units, and showed such devastating differences that referral patterns changed dramatically. Now almost 100% of children with cancer in the U.K. are treated in specialist centres.

Similar large (and unacceptable) differences were seen in a study of five centres in one U.K. city in the treatment of teratoma. The centre which saw most patients and randomized in EORTC trials had a 10% better patient survival than any of the others and for ovarian cancer, the same holds true and so on and so on. The message is unpopular with doctors who believe they know all about treatment and thus have no need for trials, and with doctors who work in district hospitals and stubbornly hold on to patients who should be referred to specialist centres. But the audience which matters consists of cancer patients, and they, armed with this information, can demand more specialists and more access to clinical trials.

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## PREVENTION OF LOCOREGIONAL RECURRENCE OF RECTAL CANCER: INTERSURGERY VARIABILITY

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In a German prospective multicentre study (1101 unselected patients operated for solitary rectum carcinoma from 7 institutions), following anterior resection or abdomino-perineal excision for cure (R0, M0) loco-regional recurrence was observed in 21.6% with an interdepartment variability between 10% and 37% and an intersurgeon variability between 4% and 55%. The frequency of loco-regional recurrences was not influenced by adjuvant treatment (used in only 15% of the patients), but was in the control of the surgeon. It was reduced by avoidance of intra-operative local tumor spillage and local radicality, in particular total mesorectum excision in each carcinoma of the middle and lower third. The best method to prevent loco-regional recurrences is good surgery.

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## QUALITY OF SURGERY

*C. McArdle*

Local recurrence is a major cause of morbidity and mortality following apparently curative resection for colorectal cancer. The overall local recurrence rate is approximately 20%; there is however considerable variation amongst individual surgeons. After correction for stage of the disease at the time of the presentation these differences persist.

Pathological studies have shown that the presence of lateral resection margin involvement is associated with the subsequent development of local recurrence. It is therefore tempting to believe that surgeons with a high turn over may achieve better results. Analysis of over 4,000 patients undergoing colorectal cancer surgery suggests that this is not necessarily