front-line strategies for high risk patients, if proven useful in the ongoing randomized clinical trials
(2) Some new "predictive" molecular markers will hopefully assist the medical oncologist in selecting patients who need aggressive therapies
(3) Some of the studies that currently evaluate the clinical potential of new agents, such as pure antioestrogens, liarozole, Capecitabine, Caelyx, Gemcitabine ... will clarify their role in the management of breast cancer
(4) Entirely new therapies, interfering with signal transduction or angiogenesis pathways will be assessed as an adjunct to chemotherapy and hormonal therapy

All these innovative drugs or strategies will be discussed.

977

A randomized single-institution study of high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin (CTC) in apical node-positive breast cancer

S. Rodenhuis, D.J. Richel, J.W. Baars, J.H. Schornagel, J.H. Borger, C. Koning, E. Rutgers. *Department of Medical Oncology, Department of Radiation Therapy, Department of Surgery, The Netherlands Cancer Institute, Amsterdam; Medisch Spectrum Twente, Enschede, The Netherlands*

Between May 1991 and December 1995, 97 patients were included in a study of high-dose chemotherapy (CTC) in stage II or III breast cancer. All patients were below 60 years and had a tumor-positive apical axillary lymph node at infraclavicular biopsy. The conservative treatment arm consisted of 3 courses of FEC: fluorouracil (500 mg/m^2), epirubicin (120 mg/m^2) and cyclophosphamide (500 mg/m^2). Responders were randomized and went on to definitive surgery, a fourth course of FEC, radiation therapy and two years of tamoxifen. Patients in the experimental arm additionally underwent high-dose chemotherapy with cyclophosphamide (6 g/m^2), thiotepa (480 mg/m^2) and carboplatin (1600 mg/m^2), followed by blood progenitor cell (PBPC) transplantation after FEC-4. Eighty-one patients were randomized: 40 to undergo conventional treatment only and 41 to receive CTC + PBPC transplantation. With a median follow-up of 42 months, the progression-free survival for all patients was superior to historical controls, but the curves of the two treatment arms are superimposable. Evidence from randomized studies is urgently required to establish the value of high-dose therapy in the treatment high-risk breast cancer.

978

Models of environmental effects on intestinal tumour development

Harpreet S. Wasan[1], M. Novelli, J. Bee, R. Goodlad, W.F. Bodmer. *Cancer genetics & Immunogenetics Lab, Imperial Cancer Research Fund, IMM, John Radcliffe Hospital, Headington Oxford; [1]Dept. Of Oncology, Hammersmith Hospital, Royal Postgraduate Medical School, Du Cane Rd, London, UK*

Purpose: Germ-free conditions can abrogate cellular proliferative effects of diets in mice, hence differing environments might affect spontaneous tumour development *in vivo* and can be studied in the "Multiple intestinal neoplasia" (MIN) mouse.

Methods: MIN carries a nonsense mutation in the mouse *Apc* gene, the earliest genetic defect in sporadic colon tumours. Heterozygous mice develop multiple polyps by 60 days of age. Mice were reared in conventional microbiological (two different diets), Specified Pathogen Free (SPF) and totally germ free environments. They were deemed ill for sacrifice independently of tumour assessments which were done blind. The small intestine was sub-divided into equal thirds and the polyps counted and measured under a X10 dissecting microscope.

Results: SPF Mice have higher small and large bowel intestinal tumour counts (mean ± SEM: conventional 21.4 ± 1.25 & 1.8 ± 0.21 *Vs* SPF: 33 ± 1.27** & 3.6 ± 0.32** respectively), which also reflected in their reduced survival (231.3 ± 9.5 *Vs 184.3 ± 5.0* days**). The terminal ileum accounted for the majority of the small bowel effect. Effects of dietary Fat showed similar increases in tumour number and also caused tumour enlargement. To date (n = 5) in totally germ-free MIN, there has been complete suppression of colonic tumour formation with no obvious small bowel effects. **$P < 0.01$.

Conclusions: The micro-environment can be manipulated both by microbiological and dietary means with powerful influences on early colonic tumour development. These effects will be discussed in the context of other micro-environmental modifiers which may lead to novel therapeutic approaches.

979

Hereditary nonpolyposis colorectal cancer is preventable

Albert de la Chapelle. *Department of Medical Genetics, University of Helsinki, Finland*

The claim that these cancers are preventable, or at least detectable at an early stage, stems from a 10 year clinical screening program in which mortality from cancer was significantly reduced in members of hereditary nonpolyposis colorectal cancer (HNPCC) families who are at 50% genetic risk of being carriers of predisposing gene mutations (Järvinen et al. *Gastroenterology* 1995). Clinical screening and preventive measures should ideally be offered only to those family members who are mutation positive and avoided in those who are negative. This can now be accomplished through efficient mutation detection. Thus cancer prevention can be accomplished in *known* HNPCC families. However, a major challenge is that most HNPCC cases are presently undiagnosed. In this presentation a strategy is proposed by which patients newly diagnosed with colorectal or other HNPCC cancers can be relatively efficiently and reliably screened for HNPCC. In a pilot study of 500 such patients, 10 new cases of HNPCC (2%) were diagnosed in this way. These developments raise the possibility that, under certain general conditions, all newly diagnosed "sporadic" patients can be molecularly screened for HNPCC.

980

Epidemiology and screening of colorectal cancer

J. Faivre. *Registre des Cancers Digestifs (INSERM CRI 9505), University of Dijon, France*

Colorectal cancer is one of the most frequent cancers. It has been estimated in the European Union that the number of new cases was 135,000 each year. This cancer is unequally spread geographically, and is among the most frequent in Western Europe and North America. Considering the present state of knowledge, only the strategy of screening for intestinal tumours at their asymptomatic stage could reduce a problem such as colorectal cancer. Data from case-control studies provides evidence of the efficacy of screening by rigid proctosigmoidoscopy or colonoscopy. The effectiveness of screening with endoscopy has yet to be demonstrated. Compliance with such a strategy is not known. Case-control studies and randomised studies indicate that it is possible to reduce mortality from colorectal cancer in people who accept screening with faecal occult blood testing. Population-based studies rely on a biennial Hemoccult test. To be effective on colorectal cancer mortality compliance has to be between 55% and 65% in the first screening campaign, and to remain high in the succeeding ones. It has also been shown that the colorectal cancer screening strategy meets commonly accepted criteria for cost-effectiveness. The time has come to encourage colorectal cancer screening with faecal occult blood test despite the current limitations of available tests.

981

Staging and treatment of early rectal cancer

P.M. Schlag, J. Diemann. *Robert-Rossle-Hospital and Tumor Institute Surgery and Surgical Oncology, Lindenberger Weg 80, 13122 Berlin, Germany*

Improved understanding of the biological features of rectal cancer and advances in diagnostic and surgical procedures result in an increased number of sphincter preserving operations in lower rectal tumors. The relevant diagnostic and treatment strategies along with their indications will be presented and analyzed.

New methods in preoperative staging with the use of three-dimensional endorectal ultrasonography which provides previously unattainable scan plans, the high-resolution magnetic resonance tomography by using an endorectal coil and the 3-D multi tissue CT-reconstruction enables the visualization of local tumor spread. These techniques improve therapy planning in rectal cancer by selecting patients for alternative therapeutical methods.

New local surgical techniques including transanal endoscopic microsurgery have been proven to fulfill radical oncologic guidelines for patients with early rectal cancer (uT1-2, G1-2).

Among the radical approaches an ultralow anterior rectal resection with colon-pouch creation and a coloendoanal anastomosis make it possible to extend the resection line to the ano-rectal junction without loss of continence.

Recently, a continent perineal colostomy has been developed. This technique can be used in cases where the removal of the rectal sphincter is

necessary for oncological reasons. Reconstruction of the sphincter function is achieved using a seromuscular cuff. This procedure avoid an abdominal colostomy. The neosphincter can also be formed secondarily, after a prior abdominoperineal excision with transabdominal colostomy. Quality of life will be improved, especially if an artificial anus can be avoid.

982

Radiotherapy of early localised rectal cancer

J.P. Gérard, P. Romestaing, F. Mornex, J.M. Ardiet. *Service de radiothérapie, C. H. Lyon-Sud, France*

Purpose: To evaluate the role of radiotherapy alone for cure in the treatment of "early" rectal cancers with 2 different approaches.

Patients and treatment: Between 1980–96, 149 patients divided in 2 groups. *Group A:* 106 pts with T1 and early T2N0 treated with endocavitary irradiation alone. Median dose of contact x -ray 95 Gy (4–5 fractions) and iridium 192 implant as a boost in 29 pts (25 Gy/1 day). *Group B:* 43 pts with T2-3 NO-1 in inoperable patients treated with contact x-ray (70 Gy/3 F) followed by external beam radiation therapy: 39 Gy/13 F/17 days + 4 Gy concomitant boost and iridium 192 implant (20 Gy/1 day).

Results: *Group A:* overall and specific 5-year survival was 83% and 94%. LOCO-regional failure were seen in 15 pts (12 were salvaged). *Group B:* overall and specific 5-year survival was 68% and 74%. Loco-regional failure were seen in 32 pts (72%). no grade 3 complication was observed.

Discussion: Surgery remains the basic treatment of rectal cancer. In highly selected cases irradiation alone can cure early T1-2 NO tumors and in inoperable patients some larger T2-3 tumors.

[1] Ref. J.P. GERARD Int. J. Rad. Oncol. BP (1996) 34: 775–83
[2] Rad. Oncol. 1996-38: 131–37

983

The surgeon and surgical procedure as a prognostic factor

John Northover. *ICRF Colorectal Cancer Unit, St Mark's Hospital, Harrow, Middlesex HA1 3UJ, UK*

The outcome of surgery for colorectal cancer varies between surgeons. Although there may well be selection bias in the cohort studies which indicate this effect, some single institution data exist to support this contention. The range of difference between surgeons in post operative complications, local recurrence and survival is larger than any likely effect of presently available adjuvant therapy.

Assuming no selection bias, surgeon variation must be due to differences in surgical technique sufficient to translate into different outcomes. Despite the likely size of this effect there have been almost no prospective randomised studies in this field. At present the two areas of technique which may be important variables are extended pelvic lymphadenectomy, as promulgated mainly by Japanese surgeons, and Heald's technique of total mesorectal excision. It is likely that both these approaches contain all the elements of best surgical practice; it is also likely that they are more radical than is necessary to produce optimum oncological outcome, with functional side effects that might be avoidable by lesser procedures It should be a matter of high priority for surgeons to design and perform prospective comparative trials to answer some of these important questions.

984

Camptothecins

Axel-R. Hanauske, III. *Department of Medicine, Klinikum rechts der Isar der Technischen Universität München, FRG*

Camptothecins (C) are a new class of antitumor compounds which act through inhibition of topoisomerase I, an enzyme crucial for changes in the topology of DNA during replication. The initial step for the induction of cell death by these agents is the formation of a stable DNA-drug-topoisomerase I complex (DDTC) during S-Phase. A fork-collision model has been developed to explain cell cycle phase specificity and implies the irreversible arrest of moving replication forks by the DDTC. Although the parent compound camptothecin showed promising activity in preclinical models, subsequent clinical trials yielded unacceptable toxicities Subsequently, analogues [irinotecan (CPT-11), topotecan, GI 147211, 9-amino-camptothecin, 9-nitro-camptothecin] have been developed and are now in various stages of clinical evaluation. Oral formulations of C are also under investigation. CTP-11 is clinically active against colorectal cancer and is currently evaluated in combination regimens. Topotecan and GI 147211 are active in ovarian and small-cell lung cancer. 9-amino-camptothecin and 9-nitro-camptothecin are currently being evaluated in Phase I trials. Other analogues are in preclinical evaluation. C are promising new agents with a unique mechanism of action, peculiar clinical pharmacology, and widespread clinical activity which will become part of the standard armamentarium of the practicing oncologist in the future.

985

Marine organisms – Are they a worthwhile source?

S.B. Kaye. *CRC Department of Medical Oncology, University of Glasgow, UK*

Forty years ago, Pettit and colleagues began a search for novel antineoplastic agents in marine organisms, which represent a life form of extraordinary longevity (over 3 billion years). Cancer is unknown in these animals, and the hypothesis is that their survival results from the evolutionary development of complex chemical protective agents with potent antiproliferative activity. More recently this search has been extended by specialist companies such as Pharma Mar SA. A large number of peptides have been isolated from a range of organisms, including the tunicates, sponges, bryozoans and algae, and shown to possess a high degree of antitumour activity in preclinical screens, including those involving human tumour xenografts. Several compounds have already reached clinical trial. These include the protein kinase C modulating agent bryostatin I, which was found in Phase I trials to have activity in melanoma, non-Hodgkins lymphoma, ovarian and cervical cancer, the protein synthesis inhibitor, didemnin B, with activity in glioma, and the antimicrotubule agents LU 103793 (a synthetic analogue of dolastatin) and ecteinascidin-743. Toxicities seen include myalgia (bryostatin), vomiting (didemnin B) and myelosuppression (LU 103793). Bryostatin-I is the most advanced in clinical assessment, and Phase II trials are proceeding. The preliminary signs of clinical efficacy, together with the wealth of novel structures in the development pipeline, gives rise to optimism that the sea will indeed prove to be a worthwhile source of anticancer agents.

986

Matrix metalloproteinase inhibitors

J. Verweij. *Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands*

Matrix metallo proteinases (MMPs) function in the degradation of extracellular matrix proteins that constitute connective tissue. In cancer there appears to be a local and temporal imbalance between the levels of activated enzymes and their inhibitors. This imbalance results in a break-down of the extracellular matrix. Degradation of the extracellular matrix is necessary when invasive tumor cells penetrate tissues, gain access to blood vessels, exit blood vessels and colonize distant sites. Thus, inhibition of the process might result in prevention of cancer progression. For this purpose synthetic matrix metallo-proteinase inhibitors (MMPIs) have been developed. In preclinical studies they were shown to inhibit organ colonization by tumor cells as well as lymphatic spread. The resultant was increased survival. In addition, there are data that MPIs are additive to the effect of cytotoxic drugs. Clinical studies up to now have been limited. Local intraperitoneal or intrapleural administration of batimastat resulted in postponement of necessary drainage procedures, but especially the intraperitoneal application was limited by to local side effects. For this reason, the present focus is on MPIs with appropriate oral bioavailability. Marimastat is the first example of an orally available MPI that was extensively studied, CGS 27023A recently also entered clinical studies. Efficacy data on MMPIs will be reviewed.

987

Compounds inhibiting angiogenesis

L.Y. Dirix. *University Antwerp, Department of Medical Oncology, Belgium*

The dependency of tumour growth on a vascular supply is established. Shutting off the supply route would lead to tumour necrosis, preventing its development would lead to growth inhibition, both at primary and secondary sites. Accessibility of vessels for systemically administered compounds, the small (or absent?) chance of resistance development and the projected limited toxicity of agents directed at a quiescent cell population, are highly promising. These two types of anti-vascular treatment need to be distinguished. The first aims at selective tumour vessel destruction and