611

Possibilities of gene therapy and radiotherapy

Jean Bourhis. *Radiothérapie, Institut Gustave Roussy, rue C. Desmoulins 94800 Villejuif, France*

Several experimental studies have shown that the efficacy of radiation therapy on tumor cells could be improved by gene transfert. One of the first approach consisted to increase radiation-induced apoptosis by targeting some genes involved in the regulation of apoptosis. Indeed, the transduction of wild type p53 gene via an adenovirus has been shown, *in vitro* and *in vivo*, to marquedly increase radiation sensitivity in various p53 mutated human carcinoma cell lines. A second approach consisted of targeting genes involved both in radiation-induced double strand break DNA repair and radiation sensitivity (DNA-PKcs/Ku70–86 genes). Some other aspects have been recently developped such as the use of radiation-inducible promotors (tPA or EGR1). The combination of such promotor with a gene able to modulate radiation sensitivity may allow to have a temporal and spatial control of the transgene expression by radiation, as shown recently with the EGR1-TNFα construct. Another approach has been proposed for the transgene expression, using a anaerobic clostridium vector, thus targeting selectively hypoxic radioresistant areas in the tumor. In conclusion, preliminary results of combining radiation therapy with the transfert of genes able to modulate radiation sensitivity are promizing and this approach certainly needs further investigations.

612

Clinical use of multi-segment intensity modulation

Benedick A. Fraass. *Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor, MI, USA*

Purpose: The use of intensity modulated radiation therapy (IMRT) has become an important research topic in recent years, however, clinical application of IMRT has been limited. This work reports on nearly four years of clinical experience with multi-segment IMRT.

Methods: More than 100 patients have been treated with multi-segment IMRT using automated and non-automated treatments with MLC-equipped treatment machines.

Results: Multi-segment IMRT has been useful for high dose conformal treatments at sites including brain, head and neck, lung, prostate, and liver. With computer-controlled treatment delivery, such treatments can be performed accurately, quickly, and effectively. The presentation will describe required treatment planning tools and methods, and will analyze the possibilities for improved dose distributions, improved target volume coverage, improved NTCPs, as well as quality assurance and commissioning requirements.

Conclusion: Multi-segment IMRT is within technical reach of many in the radiotherapy community, and can provide significant improvements over normal conformal therapy approaches. *Supported in part by National Institutes of Health Grant P01-CA59827.*

613

Towards prediction of radiosensitivity

A.C. Begg. *Division of Experimental Therapy, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands*

The three radiobiological factors of tumors which have shown to be associated with the chance of local control after radiotherapy are proliferation rate, degree of hypoxia, and intrinsic radiosensitivity. To maximize the chance of accurate outcome prediction, all three should be measured, along with known clinical predictors. This has not been achieved to date for technical reasons but remains an important goal. This paper will concentrate on ways to measure one of these; radiosensitivity.

The most direct assay is that of clonogenic survival, but is technically difficult and is takes several weeks to complete, making it an unlikely candidate for routine clinical use. Several indirect assays for cell kill exist, including those for DNA and chromosome damage, each of which can be measured by a variety of techniques. No assay has a one to one relationship with cell kill for tumor cells, although several have shown reasonable correlations, suggesting their use as clinical predictors. Their advantage is an assay time of at most a few days, allowing tests to be completed before the start of radiotherapy.

There has been recent rapid progress in the cloning and understanding of genes affecting sensitivity to ionizing radiation, leading to the hope that screening a panel of such genes for expression, function or mutation would lead to prediction of intrinsic radiosensitivity. Genes of interest are those involved in DNA repair by end-joining, including the DNA-PK complex and XRCC4, those involved in repair by recombination, including the rad52 group homologs, and the ATM gene. Present knowledge of these will be discussed. Prediction by "gene screening" is still not possible because of the complexity of the response to radiation, but there is hope that this will become feasible in the near future.

614

Is cisplatin–taxol (PT) the standard treatment in advanced ovarian cancer. The NOCOVA

K. Bertelsen, J. Kaern, E. Simonsen, M.J. Piccart, G. Hoctin Boes, P. Timmers, J.A. Roy, S. Peccorelli, N.C.I.C.G. Stuart, K. James, J. Cassidy, S. Kaye. *Odense University Hosp., Department of Oncology, Odense C, Denmark*

An European Canadian study has included 680 patients with advanced ovarian cancer in a trial comparing Cisplatin/Cyclophosphamide (PC) with Cisplatin/Taxol (PT). The doses were Cisplatin 75 mg/m^2, Cyclophosphamide 750 mg/m^2 and Taxol 175 mg/m^2. Taxol was given as a 3 hours infusion. Chemotherapy was given every 3 weeks. The two groups were well balanced according to FIGO stage histologic type, grade and residual tumor.

Distribution of FIGO stage was PC stage II 7%, stage III 73%, stage IV 19%. PT stage II 6%, stage III 74%, stage IV 19%.

In the PC arm 35% had no or minimal residual tumor versus 39% in the PT arm.

The mean number of courses was 6 in both groups. Overall 62% of the patients experienced disease progression.

Final analysis for progression free survival, crude survival and toxicity are not available at the moment, but will be ready at the presentation.

615

Comparative study of intravesical instillation of epirubicin, BCG, or BCG + INH in intermediate and high risk pTa–pT1 papillary carcinoma of the urinary bladder. First results of EORTC 30911

A.v.d. Meijden, M. Brausi, W. Höltl, D. Mack, R.v. Velthoven, F. Calais da Silva, R. Sylvester, C. de Balincourt. *EORTC-GU group, Av. E Mounier 83 bte 11, Brussels, Belgium*

Purpose: To compare intravesical Epirubicin, BCG, and BCG + INH with respect to time to first recurrence, time to progression, duration of survival and incidence of side effects.

Methods: 958 patients were randomized in this phase III trial by 42 institutions, 318 to Epirubicin, 321 to BCG, and 319 to BCG + INH.

Results: Except for more frequent liver function disturbances in the BCG + INH group, no differences in adverse effects were observed. Interim data show a shorter time to first recurrence on Epirubicin ($p = 0.01$). It is too early to assess the long term results.

Conclusion: Based on this interim analysis the addition of INH does not appear to reduce the incidence of BCG side effects while it does increase liver function disturbances. Epirubicin is associated with a shorter time to first recurrence.

616

Neo-adjuvant chemotherapy in adult soft tissue sarcoma. EORTC Protocol 62847

E. Gortzak, A. Azarelli, A. Santoro, A. Ezzat, J. Buesa, M. Van Glabbeke, A. Kirckpatrick, J Verweij. *On behalf of the EORTC Soft Tissue and Bone Sarcoma Group, Muzenplein 7 1077 WC Amsterdam, Holland*

Purpose: Patients with a "high risk" soft tissue sarcoma, as defined in trial 62771, have 50% chance of developing distant metastases, with subsequent poor survival. The value of neo-adjuvant chemotherapy was tested in a randomized phase II to test the feasibility and accrual-rate to start a phase III study with endpoints overall- and disease-free survival.

Study-Design: Patients with a high risk soft tissue sarcoma were randomized in two arms: three cycles of doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 followed by surgery +/– radiotherapy versus surgery +/– radiotherapy alone.

Results: Between April 1986 and May 1995 150 patients were entered; 134 patients were eligible. Male/female ratio: 3/2; median age 53 years. Both arms balanced for eligibility, stratification and localisation of the tumour. In

the chemotherapy arm 90% completed three courses of chemotherapy. 30% showed complete or partial remission; 50% showed stable disease; 20% showed progression. Median dose intensity was 98% (85%–106%) (In both arms radical margins were obtained in 90%. Preoperative chemotherapy did not increase surgical or radiotherapeutic morbidity.

137 eligible patients could be analyzed, at a median follow up of 4.5 years, for overall and disease-free survival.

No significant statistical difference was found for either overall survival or disease-free survival between the two arms. (p = 0.35 and 0.37 resp.)

Conclusion: The chemotherapy-regimen was feasible; the accrual was too slow. No long term benefit was shown with this regimen. Adjuvant chemotherapy in soft tissue sarcoma should only be studied in trials.

617

Achievements in the treatment of acute myelogenous leukemia (AML)

R. Zittoun. *for the EORTC Leukemia Cooperative Group; Service d'Hématologie, Hôtel-Dieu, 75181 Paris Cedex 04, France*

The induction and post-remission treatment in AML has been progressively intensified, this intensification being made tolerable by progresses in supportive care. Thus, the complete remission (CR) rate has increased from 60 to 70–80% in patients aged less than 60 yrs, most CR being achieved after a single induction course. The 5 yrs disease-free survival (DFS) is now between 30 and 50%, according to prognostic factors and post-CR treatment protocol. The overall survival (OS) is around 30%, all cooperative groups having the same level of achievement. The main treatment options, intensive chemotherapy, autologous stem cell transplantation and allogeneic BMT are currently assessed by EORTC and other groups.

In the elderly, the prognosis is far worse, due to host and tumor-related factors, with a 5 yrs OS not higher than 5–10%. Specific clinical trials are designed by the EORTC group, exploring the value of more intensive treatments in the elderly along with hematopoietic growth factors, and of maintenance treatment.

The main objectives in the future will be to overcome multiple drug resistance, to target cytotoxic drugs, to reduce morbidity of transplantation, and to control the leukemic cell regrowth through the use of various cytokines.

618

Genetic and cytogenetic alterations in ovarian cancer

T. Bauknecht. *Department of Obstetrics and Gynecology, University Hospital of Freiburg, Germany*

Purpose: Molecular genetic alterations on ovarian tumorigenesis have been identified recently. Approximately 90% of ovarian cancer are sporadic forms, 10% are estimated to be carriers of an ovarian/breast cancer susceptibility gene; these women are found primarily in families characterized by multiple cases of the early onset of ovarian cancer syndromes. Cancer susceptibility genes such as BRCA1 and BRCA2 have been recently identified and cloned.

Methods: Genetic and cytogenetic evaluation of ovarian cancer has utilized techniques including *in situ* hybridization, mutation and sequencing studies.

Results: Cytogenetic studies in sporadic ovarian cancer demonstrate in approximately 50% of cases chromosome abnormalities, 40% of those reveal clonal and 10% nonclonal changes. Disruption of chromosomes as numerical or structural changes involve most frequently chromosome X, 1, 2, 6, 7, 11, 12 and 19. However, detailed cytogenetic karyotype information is limited. Competitive *in-situ*-hybridization (comparative genome analysis [CGH]) demonstrates DNA gains of chromosomes 8q, 3 p, 20 q, 1 p, 19 p, 1 q, 12 p, 6 p, 2 q and losses on 18 q, 4, 13 q, 16 q as an indication for consistent chromosomal abnormalities and genetic instability. Germ line mutations of BRCA1 (80%) and BRCA2 (15%) are found in families that display heritable ovarian cancer syndroms. Over 111 unique BRCA1 mutations distributed throughout the gene have been described. DNA chip-based assay are now developed to scan large genes (as BRCA).

Conclusion: The general distribution of new technologies (DNA chip) for accurate and cost-efficient detection of genetic alterations is wanted. Further research is required for families with hereditary ovarian cancer syndrom to evaluate efficacy of counselling and prophylactic efforts. In sporadic ovarian cancer detection of gene mutations with phenotype modification (i.e. drug resistance) can be used to develop new therapeutic strategies.

619

Primary cytoreductive surgery in advanced ovarian carcinoma: Is it necessary in all patients?

I.B. Vergote[1], I De Wever[2]. [1]*Department of Gynecologic Oncology;* [2]*Department of Surgical Oncology, University Hospitals Leuven, Katholieke Universiteit Leuven, Belgium*

"Optimal" cytoreductive surgery has been defined in different ways. We suggest that optimal cytoreductive surgery should be defined as no or less than 1 g of total residual tumor load after primary surgery. In some subgroups of patients the survival does not improve with optimal surgery. For instance, patients with Stage IV disease or a total metastatic tumor load of more than 1000 g prior to cytoreductive surgery have a poor survival despite cytoreduction. Patients who can not be optimally debulked primarily should be very carefully selected. We compared retrospectively 96 patients with Stage III or IV disease treated according to the above mentioned principles with 112 patients from the former time period. In the latter group 89% of the patients were debulked to less 1.5 cm largest residual tumor mass. No significant survival differences were observed between the 2 groups. The improvement in survival after interval debulking surgery reported in a prospective randomized EORTC trial is encouraging (NEJM, 1995, 332: 629). Based on the total metastatic tumor load, the presence of Stage IV disease or of uncountable peritoneal metastases, etc., it may be possible to select patients for whom upfront chemotherapy followed by interval debulking surgery is an option. This concept needs to be tested in a prospective randomized study.

620

T cell retargeting for local and systemic control of disease

S. Canevan[1], D.R.M. Negri[1], M. Calabrese[2], V. Siliprandi[2], C. Botti[1], E. Seregni[1], M.I. Colnaghi[1], G. Bolis[1,2]. [1]*Istituto Nazionale Tumori, 20133 Milan;* [2]*University of Milan, Italy*

Purpose: Bispecific antibodies (bsmAbs) with specificity for a tumor target antigen on one arm and a lympho/monocyte activation molecule on the other represent new reagents able to target cytotoxic immune cells to tumors and offer a promising means of killing minimal residual disease (mrd) without adverse reactions. This type of approach is being used in numerous phase I/II trials.

Methods: Ovarian carcinoma patients with: a) intraperitoneal (ip) disease after conventional treatments, b) mrd after I line treatment and previous history of retroperitoneal lymph node involvement, c) evident tumor infiltration in lymph nodes, entered studies aimed to evaluate: a) the efficacy of ip treatment, b) the feasibility of systemic treatment and c) the localization of bsmAb-coated radiolabeled lymphocytes.

Results: Treatment with autologous activated lymphocytes retargeted with the bsmAb OC/TR resulted in an overall ip response rate of 27% with only mild and transient toxicity. The activity was mainly local and a persistent HAMA response precluded repeated treatments. The combination of iv and ip administration of OC/TR retargeted lymphocytes, which might possibly lead to an extraperitoneal cure, was feasible and clinical follow up of treated patients is ongoing. A method for radiolabeling lymphocytes was developed and localization studies are now in progress.

Conclusions and Future Directions: We expect further improvement of the retargeted-lymphocyte technology through the selection of reagents from human antibody phage libraries which will enable to repeat courses of treatment.

Partially supported by CNR-ACRO and AIRC/FIRC.

621

Ovarian cancer – Are we making progress?

T. Bjørge[1,2], A. Engeland[2], S. Hansen[2], C. Tropé[1]. [1]*Dept. of gynecologic oncology, The Norwegian Radium Hospital;* [2]*The Cancer Register of Norway, Montebello, 0310 Oslo, Norway*

Histology-specific long-term trends in the incidence of ovarian cancer and borderline tumours in Norway were examined, based on data from the population-based Cancer Registry of Norway. A total of 14,352 cases of ovarian cancer were diagnosed between 1954 and 1993, of which 94% of the histologically verified ovarian cancer was epithelial tumours. The age-adjusted incidence rate rose from 10 per 100 000 persons-year in 1954–58 to a peak of 14 per 100 000 person-year in 1984–88. In women older than 50 years, there was an increasing trend in incidence rates during the entire study period From the cohort perspective, the largest increase