Mokslas · Ekonomika · Sanglauda

Kuriame Lietuvos ateitį

Europos sąjunga

INTERNATIONAL CONFERENCE

FROM BENCH TO BED: CHALLENGES IN CANCER CARE

Dedicated to 80th anniversary of Lithuanian society of oncology

SEPTEMBER 20-21
DRUSKININKAI
2013

ISBN 978-609-95557-0-6

VILNIAUS UNIVERSITETO
ONKOLOGIJOS INSTITUTAS

Lietuvos Spindulinės Terapijos Sąjunga

LKD

CSDXDA

LOD
Lietuvos onkologų draugija

...just the unity of education, training and clinics creates the latest science-based assumptions for the oncology industry infrastructure, funding, cancer prevention, prophylaxis and new and effective diagnostic and therapeutic technologies in the health sector, that ensures highest level development of oncology services, accurate accounting of oncological diseases, a strategy of full oncological aid, diagnosis and treatment...

TODAY OUR GOAL IS TO BE A LEADER IN THE FIGHT AGAINST CANCER

DEAR COLLEAGUES,

It is my great privilege and pleasure to welcome you to the international conference „From bench to bed: challenges in cancer care“, devoted a very broad number of topics in oncology. It is of utmost importance to stress that during this event we are celebrating the 80th anniversary of Lithuanian Society of Oncology – simply stressing how deep and long are traditions of oncology in our country. I am very pleased to note that this event attracted as much as 25 international speakers from Russia, Belorus, Ukraine, Poland, Italy, Belgium, Switzerland, Germany, United Kingdom, Austria, France, Canada, USA, Taiwan.

It has been quite a tradition, that during last years Oncology Institute of Vilnius University has been organizing meetings, dealing with many specialities and subspecialties in oncology: diagnostics, surgery, medical oncology, psychooncology etc. This time we decided to cover most of the important issues in this field, thus allowing a very large number of different medical professionals to benefit from this magnificient arrangement.

Needless to remind you, that in recent years there has been a very big step in oncology worldwide: among a number of aspects, cancer diagnosis has been armed with new modalities we could only dream of several decades ago, minimally invasive surgical techniques including robotics became an unseperable part of surgical oncology, radiation therapy crossed the borders we ever though we had and today‘s cancer therapy enables us to approach cancer with diffreent targeted drugs in the light of understanding of newly discovered mechanisms. However, there is so much yet to do: some oncological diseases are still as fatal as they were, modern treatments are a huge bondage to our societies due to dramatically increasing costs, stressing further need in cancer prevention and early diagnosis.

I do hope that this unique place in our tiny Lithuania called Druskininkai under the light of soft autumn sun will help us to create a very scientific atmosphere, the meeting itself will be a start for new ideas, new thoughts and new steps in our research and practice. At the same time, social program will offer us true rechargment and succesfull return to our daily activites next week.

Yours truly –

Prof. Narimantas Evaldas Samalavičius
Director of the Institute of Oncology Vilnius University

80TH ANNIVERSARY OF LITHUANIAN SOCIETY OF ONCOLOGY

The 80th anniversary of Lithuanian society of oncology enables to summarize jobs done, which can't be undistinguished due to recognition not only in Lithuania but also on international level. The news spread by society members, practical experience- it's a basis for scientific, clinical and educational unity and development.

The success of medicine and especially oncology depends on team work, new ideas, conception, theory, diversity of opinions, experience, continuity of ideas.

It is very important input of creators of our teachers, persons who are continuing these traditions. Today celebrating anniversary we are mentioning these people: prof. L.L. Griciūte, prof. J. Didžiapetriene, prof. K.P. Valuckas, prof. D. Characiejus, prof. P. Baltrušaitis, prof. E. Moncevičiūte-Eringiene, because only due to their efforts the solid basis of oncology was founded, the new generation of high qualified clinicists, scientists was educated, who are well recognized in European science space.

Oncology society supports and continues multidisciplinary, clinical and fundamental research unity in oncology, continues the works began, makes all efforts that oncology help would be coordinated on national level, affordable and achievable for patient, that patient would get qualified, evidence based adequate help.

Today only common efforts of scientists and practicians can accelerate implementation of science into the treatment of oncological patients. Our main aim of efforts- the best treatment for our patients.

Being proud to represent Lithuanian society of oncology on her 80th anniversary, regarding to almost 400 years oncology history in Lithuania, greeting all past and present Lithuanian society of oncology members and all whose efforts help to improve our work and thanking for all invited speakers who participate in our conference, strongly believing that this international meeting will be one more significant step in fight against cancer.

Wishing creativity and nice collaboration,

Assoc. prof. S. R. Letautienė
Lithuanian society of oncology
Board chairman

DEAR HONORED SPEAKERS, COLLEAGUES,

It is my pleasure and honor to welcome you in our beautiful city Druskininkai. The occasion of our meeting is to celebrate the 80th anniversary of Lithuanian society of oncology, meet old friends and colleagues and make a new contacts. The name of the conference "From Bench to Bed: Challenges in Cancer Care" and wide variety of speakers from almost all continents shows our interests range-from socio-economical to diagnostic, different modalities of treatment. It is important to say that one day activities will be devoted to science-from gene expression, targeted drug delivery to the newest achievements in diagnostics.

Personally, I am happy that not so long ago established Association of Oncology Societies actively incorporated into the world of Oncology science and practice. We hope that this network will expands and will unite many professionals aiming to achieve one goal-help people in fight with the cancer.

We are very pleased that so many world's recognized professionals in oncology and science accepted invitation and are taking participation in our conference. It confirms that input of Lithuanian practicians and scientists is well known and valued.

The event's organizing committee and partners are dedicated to providing an outstanding experience for learning and exchange, a tradition that is consistent with all previous conferences and meetings.

On behalf of organizing committee wishing you a pleasant stay, getting new ideas for the future and new friends.

Very sincerely,

Dr. Ernestas Janulionis
Association of Oncology Societies, President

FRIDAY, SEPTEMBER 20

8.00-9.00 **REGISTRATION. COFFEE**

9.00-9.15 **CONFERENCE OPENING**
Welcome address by IOVU Director Prof. N. E. Samalavičius

9.15-9.35 **HISTORICAL ASPECTS OF LITHUANIAN SOCIETY OF ONCOLOGY**
Head of Lithuanian society of oncology
Assoc. prof. S. R. Letautienė

9.35-11.55 PLENARY SESSION
Moderators: S. R. Letautienė, E. Janulionis

9.35-10.05 **R. Sullivan (UK)**
Delivering affordable global cancer care

10.05-10.25 **S. M. Magrini (Italy)**
New technology and new drug-radiation combinations: the difficult balance between innovation and costs

10.25-10.55 **K. Thielemans (Belgium)**
Perspectives of immunology

10.55-11.25 **G. Kovacs (Germany)**
Interventional radiotherapy on the H&N

11.25-11.55 **J. Lyczek (Poland)**
Different techniques of APBI: from interstitial to SAVI

11.55-12.10 COFFEE BREAK

12.10-14.10 PLENARY SESSION.
Moderators: S. Cicėnas, R. Grigienė

12.10-12.40 **Ch. Manegold (Germany)**
Lung cancer treatment: present and future

12.40-13.10 **R. Pirker (Austria)**
Challenges in molecular biomarkers in diagnosis and treatment of lung cancer

13.10-13.40 **B. Ilsen (Belgium)**
Lung cancer screening

13.40-14.10 **R. Smoliakova, V. Zarkov (Belorussia)**
Gene expression in lung ca diagnosis and treatment

14.10-15.10 LUNCH

15.10-17.10 PLENARY SESSION
Moderators: N. E. Samalavičius, E. Juozaitytė

15.10-15.30 **P. Guex (Switzerland)**
Perspectives of psycho-oncology

15.30-15.50 **J. de Mey, H. Everaert (Belgium)**
PET/CT in Oncology

15.50-16.10 **V. F. Chekhun (Ukraine)**
Adjuvant vaccine therapy in colorectal cancer patients

16.10-16.30 **J. Vermorken (Holland)**
The role of targeted therapies in locally advanced and 1st line recurrent/metastatic SCCHN management

16.30-16.50 **X. Delgadillo (Switzerland)**
Anal cancer

16.50-17.10 **J. W Nunoo-Mensah (UK)**
Multimodal approach to rectal cancer in 2013

17.10-17.25 COFFEE BREAK

17.25-18.45 PLENARY SESSION „ONCOUROLOGY“
Moderators: M. Jievaltas, A. Ulys

17.25-17.45 **A. Fedorova (Russia)**
Possibilities of new ultrasound technology – „Histoscanning in diagnosis of prostate cancer

17.45-18.05 **S. Krasny, O. Sukonko (Belorussia)**
Adequate radical treatment of bladder ca

18.05-18.25 **F. Vandenbroucke (Belgium)**
Minimal invasive percutaneous treatment procedures in oncology

18.25-18.45 **A. Merseburger (Germany)**
Emerging therapies for castrate-resistant prostate cancer: a urology perspective

18.45-19.00 DISCUSSION

19.00-23.00 DINNER

SATURDAY, SEPTEMBER 21

9.00-12.40 PLENARY SESSION „NANO-BIOPHOTONICS, IONISING IRRADIATION, CANCER AND CELL TECHNIQUES”
Moderators: R. Rotomskis, K. Sužiedėlis

9.00-9.25 **C. Dufes (UK)**
Tumour regression after intravenous administration of novel tumour-targeted nanomedicine

9.25-9.50 **H. Schneckenburger (Germany)**
3D microscopy for visualizing a cytostatic drug and probing apoptosis of cancer cells

9.50-10.15 **Shan-hui Hsu (Taiwan)**
Fluorescent QDs for efficient labeling of hepatoma cell line and mesenchymal stem cells in vitro

10.15-10.40 **F. Vetrone (Canada)**
Nanoparticles for Highly Efficient Multiphoton Fluorescence Bioimaging

10.40-11.10 COFFEE BREAK

11.10-11.30 **N. Cordes (Germany)**
3D ECM based cell culture models for studying cellular resistance to ionizing radiation

11.30-11.50 **A. Kumar (USA)**
Cell-Mediated Nanoecapsulated Drug for Targeted Delivery into Lungs

11.50-12.20 **L. Kelbauskas (USA)**
Integrated multiparameter single-cell analysis of metabolic phenotype, gene transcription levels and nuclear architecture in premalignant progression of Barrett's esophagus

12.20-12.40 **U. Riekstina (Latvia)**
Mesenchymal stem cell therapy biosafety issues

12.40-12.50 CLOSING REMARKS

12.50-13.50 LUNCH

RICHARD SULLIVAN

New Kings Health Partners Institute of Cancer Policy
(United Kingdom)

IS CANCER CARE AND RESEARCH BECOMING A LUXURY GOOD? AFFORDING CANCER IN THE 21ST CENTURY

Cancer has become one of the most intractable global diseases in both high income and increasingly in emerging economies. This complex and complicated disease has been a major focus for R&D since the 1970's. Global public sector spend on cancer R&D has reached over 16.5 billion euros and disease specific R&D activity in cancer dominates all other areas with over 14% of total global activity. Within this research activity translational cancer medicine has expanded in only 20 years to account for nearly 40% of research outputs. In parallel the direct healthcare costs of cancer now consume between 5 and 10% of high income healthcare budgets, with particular areas such as imaging and pharmaceutical costs growing at an average annual rate of over 10%. The costs of both care and research are growing beyond the ability of countries to manage and deliver cost effective R&D and national cancer plans. The vast expansion in new technologies in cancer (NME, procedures, biomarkers, etc) coupled to rapid macro-economic (especially pricing) and socio-demographic measures is overwhelming the ability of national and trans-national systems to, a) effectively translate research through appropriately powered clinical trials, and b) deliver sufficient improvements in outcomes to merit the prices now being demanded. Cancer has reached both a crossroads and is on an apparent trajectory that could see the best care and fruits of research only available to affluent sectors of society. In this lecture we will explore the roots, trajectory and solutions to this convergent crisis and ask whether cancer care will become a luxury good; and whether the p-medicine agenda really can deliver tomorrows solutions or whether this is rapidly becoming a morally bankrupt paradigm that no-one will be able to afford.

MAGRINI STEFANO M., PASINETTI N., BUBLIONE M.

Radiation Oncology Department of the University and Istituto del Radio, Spedali Civili
(Italy)

NEW TECHNOLOGY AND NEW DRUG-RADIATION COMBINATIONS: THE DIFFICULT BALANCE BETWEEN INNOVATION AND COSTS

Background: As clearly delineated in a pivotal issue of *Lancet Oncology* dedicated to appropriateness in cancer treatment (*Lancet Oncol* 2011; 12: 933–80), delivering affordable cancer care in high-income countries is becoming a major problem. This is because of the increasing costs of new drugs (in particular the so called targeted therapies), of medical technology (from laboratory/radiology diagnostic tools to robotic surgery to new radiotherapy machines), for intensive follow up schedules and for the for the care of terminally ill.

Material and Methods/Results: A review of the major sources of uncertainty in the evaluation of the appropriateness of the new radiotherapy machines and of targeted therapies +/- radiation for cancer treatment will be presented, with particular reference to some cancer types (prostate, mesothelioma, head and neck tumors). A synthesis of the problems linked with the uneven distribution of resources and of the new therapeutic tools across Europe will be presented. Then the possible solutions to obtain a fair, clinically appropriate integration of new therapeutic tools in the radiation oncologist's armamentarium will be discussed.

Conclusion: In Europe, health expenditure is rapidly rising to levels that soon will exceed the budget devoted to finance the different health systems. The driving force to ameliorate the clinical appropriateness of cancer care is represented by the oncology professionals community. To avoid what has been called "the financial toxicity of cancer treatment" (*The Oncologist,* 2013; 18:381-390), an evidence-building oncology practice is strongly needed; appropriate interventions at the educational level should be taken, also for radiation oncologists.

BART NEYNS AND KRIS THIELEMANS

Vrije Universiteit Brussel
(Belgium)

DENDRITIC CELL BASED IMMUNOTHERAPY OF MELANOMA: THE BRUSSELS' EXPERIENCE

Electroporation of DCs withm RNA encoding the full-length tumor antigens should lead to presentation of many epitopes by the patient's unique set of HLA molecules. Moreover, electroporation of DC with mRNA also allows the functional modification of the cellular vaccine. To this goal, we provide three different molecular adjuvants to immature, monocyte derived DCs through electroporation with mRNA coding for CD40L, CD70 and caTLR4 or socalled TriMix mRNA.

At our institution, clinical trials in pretreated advanced melanoma patients are being performed. These patients are treated with TriMixDC-MEL, amixture of TriMix-DC coelectroporated with mRNA encoding a fusion of DC. LAMP and 1 of 4 melanoma associated antigens (gp100, tyrosinase, MAGE-C2 or MAGE-A3).

In a pilot clinical trial, 24.10^6 TriMixDC-MEL cells were administrated solely by the intradermal (ID) route. Subsequently, a phase IB was conducted to investigate the safety of administrating TriMixDC-MEL by the intravenous (IV) and ID-route. The ratio of ID/IV administered DC was: Cohort-1: $20.10^6/4.10^6$ DC [2pts],- :$12.10^6/12.10^6$ DC [3pts],-3:$4.10^6/20.10^6$ [6pts], and--4:0/24.10^6 DC [4pts]; DC were administered 4x q2w, and a 5^{th} administration on w16. Local skin reactions (<gr1-2) were observed in all pts receiving DC ID, flu-like symptoms (<gr2) were observed in pts ID12/21 treated ID and in 8/15 pts treated ID/IV. Post IV infusion chills (gr2) were observed in 3/15 pts. Inflammatory cytokine release was documented during these chills. ID administration of TriMixDC-MEL was found to be feasible, safe, effectively stimulating CD8+ T-cell responses, but did not result in objective tumor responses. In contrast, the combined ID/IV administration of TriMixDC-MEL resultd in 2 PR and 2CR (by RECIST) out of 15 pts (BORR of 27 %; ongoing after 24+, 28+, 33+, and 34+ mths). A confirmed stable disease was documented in four additional patients (for a disease control rate of 53 %). From this study we concluded that ID/IV-administration of TriMixDC-MEL as a single-agent cellular immunotherapy is a associated with distinct but manageable side-effects and has seemingly superior clinical activity as compared to CD administrated solely ID in patients with pretreated advanced melanoma.

Ipilimumab (ipi), an anti-CTLA-4 mAb, enhances T-cell function and has established activity in advanced melanoma pts. We aimed to investigate the safety and activity of TriMixDC-MEL combined with ipi. TriMixDC-MEL was administered IV (20.10^6) and ID (4.10^6) 1h after ipi infusion (10 mg/kg), q3w for a total of 4 administrations. Maintenance therapy with ipi was allowed q12w for pts free from progression at week 24. The primary endpoint was disease control rate (by irRC). 37 pts initiated treatment. Local skin injection reactions (gr 1-2) were observed in all pts, flu-like symptoms (gr 1-2) in 20 (54%) pts, post-infusion chills (gr 1-2) in 15 (40%) pts. Immune-related averse events were observed in 29 (78%) pts [11 (29%) pts had grade 3 or 4 AEs]. Most common were dermatitis (24 pts); hypophysitis/hypopituitarism (6 pts), diarrhea (6 pts), and hepatitis (5 pts). irAEs necessitated systemic corticosteroids in 17 (45%) pts. The best objective tumor response (35 evaluable pts): 5 CR, 5 PR, 9 SD and 16 PD (disease control rate: 54%). Objective responses are currently ongoing in 6/10 pts (11+ -22+ months). This phase II study of TriMixDC-MEL ID/IV in combination with ipi demonstrantes anti-melanoma activity in over 50% of the patients with therapy resistant advanced melanoma. Further clinical development of TriMixDC-MEL in combination with immune checkpoint modulators is warranted.

Furthermore, TriMixDC-MEL is currently under evaluation in a randomized phase II trial in the adjuvant setting following resection of macrometastases.

GYÖRGY KOVÁCS

Department of Interdisciplinary Brachytherapy,
University Hospital Schleswig-Holstein Campus Lübeck
(Germany)

INTERVENTIONAL RADIOTHERAPY ON THE H&N

Classic indications for interventional radiotherapy (brachytherapy) on the head & neck were the curative and solely interstitial/mould therapy of primary T1-T2 nodal negative cancers as well, rarely, salvage treatments of small recurrent tumors in previously irradiated areas. Due to the developments in surgery (use of lasers, improved reconstruction techniques) as well radioprotection issues this entities are cured nowadays primarily by surgery. In the past years, improved brachytherapy technology (introduction of remote controlled stepping sources) and the use of advanced software solutions in treatment planning as well incorporation of modern imaging methodology (MRI, PET) offer a great potential of using brachytherapy as an effective dose escalation method with less normal tissue radiation compared to any external beam radiation technique. Furthermore, interdisciplinary cooperation with surgical specialities (head and neck surgery, neurosurgery, dento-maxillo-facial surgery, ophthalmology) lead to successful use of intra-or perioperative brachytherapy for clearance/dose escalation of surgical margins. This can lead due to lower level of external beam radiation and/or less aggressive surgery to organ and function preservation.

Some groups published clinical data showing comparable or better tumor control with improvements in functional results and in patient quality of life by using interstitial brachytherapy boost compared to different kind of modern external beam radiation techniques (+/- chemotherapy) in base of tongue/oropharynx cancer as well nasopharyngeal tumors.

Others reached remarkable function (visual acuity) preservation in advanced paranasal/nasal cavity cancers by using a multidisciplinary approach combining external beam radiochemotherapy, interstitial brachytherapy and function preservative surgery, however, prospective clinical studies on this field needs to be performed.

The use of brachytherapy for salvage in previously irradiated regions of the head and neck in combination with ablative and advanced reconstructive surgery has a great potential in a strongly selected patient cohort.

It is in the responsibility of the brachytherapy community to use this potential and drive multicentric and prospective comparative studies to be able defining and presenting the important role of modern brachytherapy in the treatment of head and neck malignancies.

CHRISTIAN MANEGOLD

Medizinische Fakultät Mannheim der Universität Heidelberg,
Chirurgische Klinik - Interdisziplinäre Thorakale Onkologie
(Germany)

LUNG CANCER TREATMENT: PRESENT AND FUTURE

It is evident to all of us that conventional chemotherapy in advanced non-small cell lung cancer has reached an efficacy plateau with great space for improvement. Therefore, many efforts have been undertaken to prolong overall survival in this setting, with some success. Nonetheless, the management of lung cancer has changed significantly during the last decade for several reasons. Our increased understanding of the molecular biology of lung cancer and its change in epidemiology has opened up avenues for treatment strategies, exemplified by terms such as customized therapy and therapeutic targeting. It is important to note that therapy individualization challenges the work of pathologists around the globe and the process of obtaining a clinically relevant tumor diagnosis. Not only histologic subtyping becomes clinically relevant but molecular information is also of increasing importance for treatment selection. Routine molecular testing in certified laboratories must be established. It is clear to the thorax oncological community that investigating and implementing therapeutic targeting in lung cancer cannot any more follow the traditional concept of clinical trials. Since the majority of large randomized phase III trials of the last decade turned out negative in their primary endpoints, the time of conducting trials on large unselected patient population is over and must be replaced by smaller trials on selected patients, and trials using study endpoints which can function as substitutes for the classical overall survival endpoint.

The recent availability of anti-neoplastic agents such as pemetrexed, the monoclonal antibody bevacizumab, erlotinib, gefitinib, as well as crizotinib has let to treatment optimization and individualization based on predictive factors such as tumor histology and molecular markers. Other products holding considerable promise for the near future include tumor vaccines, and other immunotherapeutic approaches, which have already been reached the level of clinical phase III trials.

It seems reasonable to state that the time of customizing therapy, the time of selecting specific regimens by histology and molecular biology has arrived. In patients with non-squamous tumors harboring an activating EGFR-mutation, an EGFR-tyrosine-kinase inhibitor may be the leading option of first-line therapy not only because of being active but also because of its feasibility and improved toxicity profile. In patients with non-squamous cell tumors not expressing EGFR-mutations, combination chemotherapy remains standard with pemetrexed as the preferred partner of cisplatin. Furthermore, it has been demonstrated that in non-squamous NSCLC the addition of bevacizumab to standard doublet therapy improves overall survival.

With regard to patients with squamous cell tumors gemcitabine, vinorelbine or the taxanes in combination with platinum-based agents remains the chemotherapeutic standard.

Another effort to improve survival has been related to the duration and scheduling of medical treatment. Extending treatment with one drug of the induction regimen until tumor progression has provided strong evidence of increasing survival. Treatment continuation beyond 4 cycles of combination therapy by a non-cross-resistant agent not being included in the induction therapy has also been investigated with success. Based on recent data from 3 large randomized phase III studies current international guidelines recommend maintenance therapy as a new option of medical management of advanced NSCLC for patients who have not progressed under standard induction regimens. Therefore, maintenance therapy represents an important change in the treatment algorithm of medical management of lung cancer in 2013 in general with specific implication for subsequent therapies.

ROBERT PIRKER
Department of Medicine I, Medical University of Vienna
(Austria)

CHALLENGES IN MOLECULAR BIOMARKERS IN DIAGNOSIS AND TREATMENT OF LUNG CANCER

Treatment of lung cancer is based on tumor histology, tumor stage, performance status of the patients and other parameters. Recent advances in have been based on the better understanding of the molecular pathogenesis of lung cancer. Smoking-related cancers have been found to be molecularly different from those of never-smokers. Characterization of driver mutations has led to a more detailed classification of non-small cell lung cancer (NSCLC). Knowledge of mechanisms involved in tumor growth have also stimulated research in customized chemotherapy and targeted therapies. Both strategies are based on biomarkers that allow determining the target and predicting benefit from treatment.

Histological subtypes have become important with regard to chemotherapy in patients with advanced NSCLC. Pemetrexed has been shown to be superior to gemcitabine in patients with non-squamous cell NSCLC and gemcitabine superior to pemetrexed in those with squamous cell NSCLC (1). Customized chemotherapy based on molecular biomarkers such as DNA repair enzymes has been studied in the adjuvant and palliative settings. ERCC1 and p27 were shown to predict benefit from adjuvant chemotherapy with cisplatin-based protocols in the IALT-Bio project (2, 3) but their predictive values could not be validated in the LACE-Bio project (4). KRAS status is not predictive but codon13 mutations should further be studied for their potential predictive value (5). Customized chemotherapy did not improve clinical outcome in phase III trials but is further evaluated in several phase III trials (6-8). Thus customized chemotherapy based on molecular tumor characteristics cannot currently be recommended for routine practice.

Targeted therapies require the demonstration of the presence of the therapeutic target in the tumors. Predictive biomarkers will define those patients who will derive a benefit from targeted therapies. While no clinically useful biomarkers are available for angiogenesis inhibitors, predictive biomarkers have been established for EGFR-directed therapies. High EGFR expression in tumors has been shown to define those patients who will benefit from the addition of cetuximab to first-line chemotherapy in patients with advanced NSCLC (9). High EGFR expression in tumors is seen in about 25-30% of patients with advanced NSCLC. KRAS mutations, EGFR copy numbers and EGFR-activating mutations did not predict benefit from cetuximab (10, 11). EGFR-activating mutations have been established as predictive biomarkers for EGFR tyrosine kinase inhibitors (12-15). EGFR-directed TKIs (gefitinib, erlotinib, afatinib) improved progression-free survival and quality of life compared to first-line chemotherapy (15-22). With regard to crizotinib, ALK rearrangements have been established as biomarkers (23-24). Thus patients with advanced NSCLC are now routinely tested for the presence of these EGFR mutations and ALK translocations.

Important challenges of the characterization of predictive biomarkers are heterogeneity of biomarker expression, insufficient tumor tissue for molecular analysis, determination of the most appropriate laboratory test including proper cut-off levels, and priorization of biomarker assessments. Despite these challenges, however, systemic treatments based on predictive biomarkers will become increasingly important in the future. Development of targeted agents will be accompanied by biomarker development. These developments will then further improve clinical outcome in patients with NSCLC.

References

1. Scagliotti G et al. JCO 2008, 26, 3543
2. Olaussen et al. NEJM 2006;355:983-91.
3. Filipits M et al. JCO 2007;25:2735-40.
4. Friboulet L et al. NEJM 2013, 368, 1101
5. Shepherd FA et al. JCO 2013, 31, 2173
6. Cobo M et al. JCO 2007, 25, 2747
7. Rosell R et al. ASCO 2013, LBA 8002
8. Bepler G et al. JCO 2013, 31, 2404
9. Pirker R et al. Lancet Oncol 2012;13:33-42.
10. Khambata-Ford S et al. JCO 2010;28:918-27.
11. O`Byrne K et al. Lancet Oncol 2011;12:795-805.
12. Lynch TJ et al. NEJM 2004;350:2129-39.
13. Paez J et al. Science 2004;304:1497-1500.
14. Pao W et al. PNAS USA 2004;101:13306-11.
15. Mok TS et al. NEJM 2009;361:947-57.
16. Maemondo M et al. NEJM 2010;362:2380-8.
17. Mitsudomi T et al. Lancet Oncol 2010;11:121-8.
18. Zhou C et al. Lancet Oncol 2011;12:735-42.
19. Rosell R et al. Lancet Oncol 2012, 13, 239
20. Li-Long Wu et al. Abstract 8016, ASCO 2013, Chicago, USA
21. Sequist LV et al. JCO 2013, 31 (online July 1, 2013).
22. Li-Long Wu et al. ASCO 2013, abstract 8016
23. Kwak EL al. NEJM 2010, 363, 1693
24. Shaw A et al. NEJM 2013, 368, 2385

BART ILSEN

Universitair Ziekenhuis Brussel,
Department of Radiology-Thoracic imaging
(Belgium)

LOW-DOSE CT LUNG CANCER SCREENING

In contrast to other common malignancies, screening for lung cancer was till recently not recommended. However, recent evidence suggests that low-dose computed tomography (CT)-based screening of select populations may decrease lung cancer mortality.

In this presentation we define concepts as “low-dose” CT, try to find our ideal candidates and discuss the potential benefits and risks.

R. M. SMOLYAKOVA, V. A. MATUSEVICH, V. P. KURCHIN, V. V. ZARKOV, A. M. PASHKEVICH, A. N. KURCHENKOV

N. N. Alexandrov National Cancer Centre of Belarus, Minsk (Belorussia)

MOLECULAR GENETIC EVALUATION OF ERCC1 GENE EXPRESSION IN NON-SMALL-CELL LUNG CANCER PATIENTS

The incidence of pleomorphism in ERCC1 DNA repair genes in the European population accounts for about 35%. The presence of mutations in ERCC1 DNA repair genes determines drug resistance to platinum agents, and this is taken into account when individual adjuvant chemotherapy is considered for patients undergoing radical surgery. The presence of pleomorphism AAC>AAT in codon 118 (Asn 118 Asn) of ERCC1 gene is associated with the gene expression reduction and consequently with enhancing of oxaliplatin efficacy. This makes it possible to stratify patients by drug sensitivity, to improve the effect of the therapy administered, to avoid the occurrence of side effects, to improve the quality of life. However, the opinions are currently controversial about the prognostic significance of the gene expression in lung cancer patients prior to adjuvant therapy with platinum drugs. Some authors take a favourable view of the prognostic significance of ERCC1 gene strong expression before the drug therapy. Some publications lay emphasis on clinical and prognostic significance of evaluating the gene expression in the presence of a definite pathological type of lung cancer (adenocarcinoma, squamous-cell, clear–cell carcinoma, etc.) and development of drug resistance.

The objective of this study is evaluation of ERCC1 gene expression level in radically operated non-small-cell lung cancer (NSCLC) patients prior to adjuvant chemotherapy.

Materials and methods: The materials of the study are the clinical findings of 22 stage I-IIB NSCLC patients. All the patients had pathological diagnoses.

RNA separation from the tumor tissue of lung cancer patients was performed with RNAqueous-4PCR Kit (Ambion, USA). For PCR arrangement, oligonucleotide primers and Applied Biosystems (USA) probe were used. PCR analysis was carried out on 7300 Real-time PCR system (Applied Biosystems, USA) amplifier. Quantitative evaluation of the gene expression was made using $\Delta\Delta$cT techniques. RNA 18s sequence was used for normalization.

Results: The mean age of the patients examined was 56.3 ± 10.5 years. Pneumonectomy was performed in 17.3% of NSCLC patients. Surgical interventions of lob- and bilobectomy magnitude were done in 75% and 7.7% of the patients respectively.

The prevailing pathological tumor type (59.6%) was squamous-cell carcinoma, adenocarcinoma was detected in 29% of the patients.

The results of the molecular genetic investigations demonstrated that ERCC1 gene expression level in NSCLC patients was ranged from 0.0004 to 94.5402 relative units (median 0.441 relative units).
In the group under study, 7 patients exceeded the threshold value of ERCC1 gene expression level. When analysing ERCC1 gene expression with regard for the pathological tumor type, it should be noted that the increased production of the gene was observed in 5 lung adenocarcinoma patients and in 2 cases of squamous-cell type. In 14 NSCLC patients, expression of the gene under study was lower than the threshold level (<1). One patient with ERCC1 gene expression of 0.88 relative units presented with disease progression.

Conclusion: According to the preliminary data obtained, an increased level of ERCC1 gene expression was found in 31.8% NSCLC patients, predominantly in those with lung adenocarcinoma (71.4%).

PATRICE GUEX
Lausanne Medical School, Department psychiatry
(Switzerland)

PERSPECTIVES IN PSYCHO-ONCOLOGY

According to IPOS (International Psycho-oncology Society) the mission statement of **Psycho-oncology** is to encourage "a humanistic approach" to oncology in order to "provide leadership and development of clinical standards, education and research on the psychological, social, behavioral, ethical (decision making) aspects that affect the quality of life of cancer patients and their close relatives."

This sub-specialty addresses the two main psychological dimensions of cancer: the psychological responses of patients to cancer at all stages of the disease (and that of their families and caretakers) and the behavioral and environmental factors that may influence the disease process. (Holland JC, 2003).

Psycho-oncology is a multi-disciplinary, team approach and has shared boundaries with all specialties in clinical oncology (surgical, medical and radio-oncology). It should be patient centered and responsive to each individual patient / carer / family's needs and priorities.

A critical priority is the assessment of distress as a vital sign (along with others like somatic and biological measures, and pain evaluation) in order to integrate the psychosocial domain into the routine provision of oncology care.

In this regard attention to psychosocial wellbeing should remain a priority across the cancer journey from screening through diagnosis and treatment, recurrence or transition to palliative care and cancer survivorship.

Appropriate therapeutic interventions such as psychotherapy, psychological support, cognitive behavioral therapy, or family therapy would be recommended, according to patient's level of distress, just as medical therapies are currently provided for the management of physical symptoms related to cancer and its treatments.

Ideally, a psycho-oncologist should assess every patient with cancer at the moment of diagnosis and throughout the treatment process in order to reduce distress and its associated negative effects on patient satisfaction and quality of life.

Earlier identification and intervention of distress can significantly improve patients' and families' emotional responses and adjustment issues.

Along with cultural context, and patients own life experiences, his (her) social environment and family dynamic are an important focus of psycho-oncology.
When someone has cancer, the family is affected and the family balance is disrupted (family being a unit of care facing the disease).

In return a distressed caregiver not only experiences varying degrees of physical and psychological suffering, but can also negatively affect the well-being of the patient in treatment; psycho-oncologists (psychiatrist or psychologists) are trained to discern such distress in patient and family members and recommend therapy as needed.

In addition, not only the disease itself, but also cancer therapies create a range of psychiatric and neuropsychiatric disorders. Fatigue, confusion, peripheral neuropathy, dyspareunia, infertility, incontinence, impotence, and chronic pain syndromes are complications of some medical treatments. In that way psychiatrists are assigned to work directly in the medical, gynecology, breast, prostate, and pediatric areas to provide the ideal model of psychological care integrated into the medical care.

Jimmie C. Holland. Psychological Care of Patients: Psycho-Oncology's Contribution.

J Clin Oncol (2003) 21:253s-265s

VASYL F. CHEKHUN,
HRYHORII P. POTEBNIA

RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine
(Ukraine)

ADJUVANT VACCINE THERAPY IN COLORECTAL CANCER PATIENTS

From the first steps of oncology (more than hundred years ago) one of the priority areas is the impact on the immune system. In the past nearly two decades the immunotherapy of cancer has made significant progress due to improved understanding of the underlying principles of tumor biology and immunology, which are critical in the development of immunotherapy in laboratory and its implementation in clinic. Principles that guide the development and application of immunotherapy include antibodies, cytokines, vaccines, and cellular therapies. The goals of cancer vaccination are to activate and expand tumor-specific T cells as effective means of augmenting immunity. To induce powerful antitumor immune response, peptides derived from tumor-associated antigens (TAAG), must be presented to T cells. Therapeutic vaccinations are designed to enhance preexisting immunity or induce novel, strong antitumor immune responses in patients with cancer. Vaccine strategies include the use of peptides derived from TAAG, whole tumor cells, TAAG-encoding DNA, or viral carriers alone or with in vitro generated dendritics cells, that are the most potent antigen-presenting cells, capable of activating naive and memory T cells.

The possibility of using biotherapy in the treatment and prophylaxis complex in colorectal cancer (CRC) is one of the current issues of widely spread studies in different countries. In our Institute (IEPOR) studies on construction of various types of cancer vaccines (CV) for antireccurent and antimetastatic treatment/prophylaxis are conducting during some decades. CV, designed in IEPOR that is based on autologous tumor cells, obtained after surgical tumor removal, and products of synthesis of B. subtilis B-7025, is approved for clinical usage in Ukraine for treatment various solid tumors. The mechanism of therapeutic action of this vaccine is as following - stimulation the activity of mechanisms of antitumor immunity: it increases the activities of natural killer cells, specific T lymphocytes, the level of complement-dependent cytotoxic antibodies, general activation of the immune system (increase of the proliferative index of central and peripheral immunity organs, which indicates the involvement in the immune process of mononuclear phagocytes (dendritic cells) with the subsequent stimulation of the lymphoid tissue. The use of the this vaccine in the postoperative period reduces the viability of the remaining tumor cells and thereby prevents/slows the development of metastasis and recurrence. In terms of efficacy and safety of application IEPOR vaccine is in accordance with international standards of specific immunotherapy of tumors. Autologous tumor-based vaccination has led to successes in the treatment of CRC. Adjuvant vaccine therapy of CRC patients with IEPOR antitumor autovaccine initiates the elevation of T-lymphocytes and active level of key cytokines, normalizes the immune status of the patients, improves life quality and increases the efficiency of treatment in patients with II-III stages, reduces the likelihood of recurrence of the disease, increases 5-year survival rate by 10–14%. The IEPOR vaccine usage in CRC patients increased the 5-year survival vs those CRC patients that did not receive vaccination: overall survival - 88.37% vs 74.44%; relapse-free - 79.67% and 63.91%; in patients with metastases in regional lymph nodes (T3-4N1-2M0) - increased on 28.6%.

We consider that IEPOR vaccine in complex treatment with adjuvant chemotherapy is an effective treatment regimen. As the long-term safety profiles of therapeutic CV are established, they probably will be used in patients with high risk of cancer, such as those with familial adenomatous polyposis, who are at risk for the development of CRC, and it might be the prototypic cancer for which successful immunotherapy of other gastrointestinal malignancies is based. The development of strategies for combining immunotherapy with cytotoxic and molecularly targeted agents for future multimodal cancer therapy will enable even greater progress and ultimately lead to improved outcomes for patients receiving cancer immunotherapy.

XAVIER DELGADILLO PFENNINGER

Coloproctology Unit, Clinique Montbrillant, La Chaux de Fonds (Switzerland)

ANAL CANCER

Introduction.- Anal Cancer (AC), an uncommon malignancy with an increasing incidence is a worldwide disease attributed to a large homosexual male population.

Anatomy and aetiology.- Both chapters are discussed about their strong association to Human Papilloma Virus infection (HPV) and AC. Classification of AC is based on the World Health Organisation /WHO's table provided and described in detail at the oral speech. An special description is made about the Squamous Cell Carcinoma (SCC) as the commonest AC. Symptoms, clinical findings and diagnosis are careful mentioned and precise description made for the staging of the lesions.

Features.- Special mention is appointed about the treatment for all AC, SCC and other neoplasia, including Radiotherapy, following the Staging method devised by the American Joint Committee on Cancer. Diverse combined modality therapy, chemotherapy and drugs involved like 5-FU and mitomycin C and finally the treatment of distance nodal disease and the management of residual and/or recurrent disease in the anus, as described by Hyder and Cunninham since 2011.

Final topics.- A particular description is made about Adenocarcinoma of the anal canal, the Bowen's disease, Paget's disease, malignant melanoma. Emphasized discussion will be held about the Anal intraepithelial Neoplasia (Tis) also known as AIN as described by McCance et al. late in the 80's.

Imaging.- Fully imaging of lesions and tables will be available under demand or asked solicitation on Power Point slides. References are submitted also.

JOSEPH NUNOO-MENSAH

Colorectal & Laparoscopic Surgeon King's College Hospital, London (United Kingdom)

MULTIMODAL APPROACH TO RECTAL CANCER IN 2013

In the last century, the treatment of rectal cancer has changed dramatically. Once considered an incurable disease, combined modality therapy has improved mortality from 100% to less than 5%. At the same time, the risk of locally recurrent disease, once seen in over 30% of patients and associated with a horrible fate, has been reduced to less than 5% in recent years. This dramatic reduction paralleled surgical techniques based on a growing understanding of anatomy, disease pathology and the introduction of combined modality therapy regimens.

Prior to the mid-1980s, patients with rectal cancer usually underwent surgery alone, resulting in high rates of pelvic failure with subsequent morbidity and death. Trials from the 1980s to 1990s showed that postoperative chemoradiotherapy decreased pelvic failure rates and improved survival, leading to its incorporation into the routine management of patients with resected stage II/III disease. A growing European surgical experience showed that total mesorectal excision (TME) alone resulted in high rates of local control, demonstrating the importance of surgical technique in reducing pelvic failure and raising the question of the need for radiation therapy. However, a large randomized trial from the Netherlands demonstrated that patients receiving preoperative radiation therapy and TME had significantly lower rates of pelvic relapse vs patients undergoing TME only. Follow-up analyses of this trial have further shown that node-positive patients undergoing TME alone experience pelvic failure rates exceeding 20%. More recently, the German Rectal Cancer Study demonstrated that preoperative chemoradiotherapy (vs postoperative therapy) leads to superior pelvic control and sphincter preservation, as well as lower rates of acute and chronic toxicity. Using the approach of preoperative chemoradiotherapy and TME, pelvic failure rates are now less than 10%. Based on these study results, the standard of care for patients with rectal cancer patients in Europe (European Society of Medical Oncology (ESMO) Consensus Guidelines in 2012) and the United States (National Comprehensive Cancer Network (NCCN) guideline version 4.2013 rectal cancer) now exists.

While carcinologic outcome for conservative operations has improved over the last years, the outcome for Abdominoperineal resection (APR) remains poor, with high local recurrence rates, up to 30%, in spite of aggressive adjuvant therapy. This may be explained by technical difficulties encountered during APR, resulting in tumor perforation and positive circumferential margins but, perhaps, also, because of the more aggressive characteristics of the tumors that require APR. This has led to the recently re-introduction of the

concept of the extralevator abdominoperineal excision (ELAPE) to provide a large cylindrical excision.

Complete pathological response to neoadjuvant chemoradiotherapy has gained considerable attention during recent years. In single institutional reports complete pathological response has been found in 0-40% of cases treated for cure. A 'watch and wait' policy has been proposed, which avoids immediate surgery and its morbidity and mortality. However presently, there are no reliable predictors for patients achieving a pathologic complete response to neoadjuvant therapy, pelvic recurrences may be difficult to detect and/or salvage, and relapses may occur many years post treatment i.e. beyond 5 years.

Looking beyond 2013, advances in the treatment of rectal cancer will aim to address the following issues.

Will the logical step be the incorporation of new chemotherapeutic/targeted agents into a neoadjuvant combined-modality approach to rectal cancer?

Will the integration of new radiation technologies including PET-based treatment planning, intensity-modulated radiation therapy, proton therapy, and image-guided radiation therapy decrease acute and long-term complication rates without affecting local control rates, and will it be possible to escalate radiation doses safely with these techniques?

Will the identification of molecular prognostic markers allow 'customization' of treatments?

Do all patients with rectal cancer require surgery after neoadjuvant therapy, and do all patients require radiation therapy?

Can positron-emission tomography (PET), other imaging modalities, and molecular markers more accurately predict for pathologic complete response and long-term disease-related outcomes?

Does an increase in response rate translate into improved local control and survival?

Is postoperative adjuvant chemotherapy necessary for all patients following preoperative chemoradiotherapy?

ANNA FEDOROVA

President Medical Clinic, Moscow
(Russia)

POSSIBILITIES OF NEW ULTRASOUND TECHNOLOGY – HISTOSCANNING IN DIAGNOSIS OF PROSTATE CANCER

Histoscanning of a prostate is a new ultrasound method, which reveals the presence of cancer in the prostate using computer analysis of native reflected ultrasound signals from cells of the entire volume of prostate gland. As a reference value for evaluation of histoscanning results is used a volume of pathological signal intensity 0.5 cc. So, a presence of a lesion can be defined as a HistoScanning positive volume bigger than 0.5cc, and it is possible to accurately estimate the volume of tumor lesions, and their spatial orientation on three-dimensional model of a prostate.

Construction of the initial or basic three-dimensional ultrasound image of a prostate is performed on a standard ultrasound scanner by automatically rotating of endocavital biplane transducer along the axis of rotational movement of transducer. The transducer collects the image in two projections: sagittal and frontal, and transmits all collected information during the study on a separate computer with a histoscanning program (Pic.1). Then an analysis of obtained during scanning information is performed by a virtual modeling and selection of suspicious lesions on the three-dimensional model of a prostate.

Pic.1 Imaging system for histoscanning technology: A - Standard ultrasound scanner with the ability to simultaneous target biopsy of the prostate, B - Endocavital radiation sensor, rotary displacement sensor system C – Histoscanning mashine

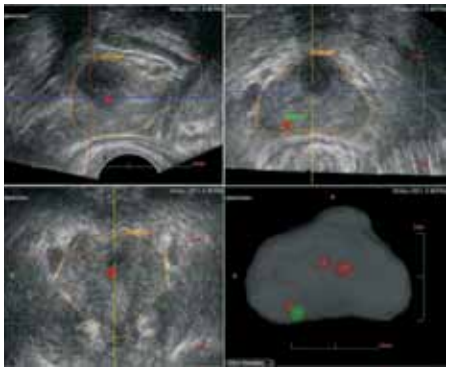
Image acquisition in three different planes of scanning provides more accurate information about the volume of cancer area, and more accurately establish the localization of the tumor process, especially areas, which are difficult for targeted biopsy.

Histoscanning technology has been tested in many world-famous foreign clinics, where studies have been performed on large groups of patients and further analysis showed high statistical results.

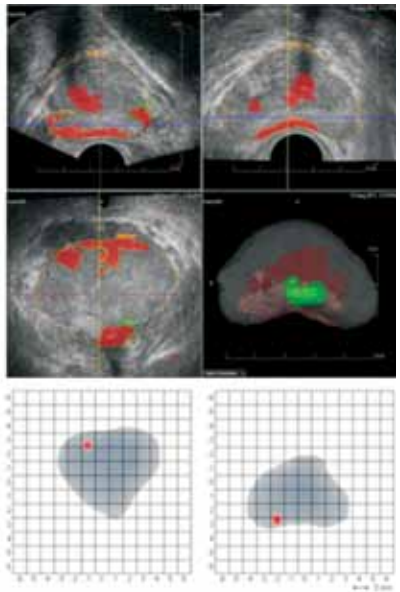
Foreign studies demonstrate a very high sensitivity of histoscanning, which is from 90 to 100 percent. In our study, we obtained almost high sensitivity and specificity of a method, by observing 150 patients with suspicion on prostate cancer. Histoscanning results were compared with pathomorphological data, received after biopsy and radical prostatectomy based on the presence and location of the tumor.

By our opinion, main diagnostic possibilities of histoscanning are - accurate detection and localization of cancer cells, possibilities to detect cancer cells in the central zone, examining patients after hormonal/radiation therapy and Examination of patients after radical prostatectomy for recurrence of the process.

In conclusion, Histoscanning is a non-invasive and sensitive technique to better define prostate cancer, which can be used for screening. Can reduce the number of unnecessary biopsies and to avoid repeat biopsies. Can also identify cancer cells in the central part of the prostate and along prostatic urethra. Can be used for planning biopsy studies, and can be very important in the decision to perform other invasive procedures on prostate gland.



Pic 2 Histoscanning results in case of normal prostate gland tissue.



Pic 3 Histoscanning results in case of prostate cancer: high intensity signal in the peripheral part and at the apex.

KRASNY S. A., SUKONKO O. G., POLYAKOV S. L., ROLEVICH A. I., MINICH A. A.

N. N. Alexandrov National Cancer Centre of Belarus, Minsk (Belorussia)

PREDICTORS OF MAJOR COMPLICATIONS AFTER RADICAL CYSTECTOMY WITH URINARY DIVERSION

ITRODUCTION: Radical cystectomy with urinary diversion is a major procedure with reported complication rate 20-60%. Minor complications are manageable, while major complications may have significant influence on treatment outcome. The aim of the study was to assess burden of cystectomy-related complications and to define prognostic factors of major complications.

MATERIAL AND METHODS: We retrospectively analyzed complications after radical cystectomy performed in our institution between 1999 and 2008 in a total of 408 patients. Urinary diversion types were: orthotopic neobladder (n=335), ileal conduit (n=51) and continent ileal pouch (n=22). All complications were reviewed and graded according to modified Clavien classification system. Univariate and multivariable logistic regression analyses were used to evaluate variables associated with major complication defined as grade 3 and more.

RESULTS: A total of 132 complications occurred in 91 patients. Overall 22% of patients experienced one or more complication: 63 (15%) pts had one complication, 20 (5%) – two complication and 8 (2%) patients – more than two complications. There were 26 (20%) Clavien grade I, 39 (30%) grade II, 48 (36%) grade III, 5 (4%) grade IV and 14 (10%) grade V complications. A univariate analysis found only body mass index (BMI) as significant predictor of major complication (OR=2.08; 95% CI 1.03-4.18; p=0.041). Type of urinary diversion (orthotopic vs other, p=0.060) and surgeon experience more than 100 cystectomies (p=0.072) trended toward significance. In multivariate analysis, BMI>25 (OR=2.62; 95% CI 1.23-5.55; p=0.012) and surgeon experience (OR=0.48; 95% CI 0.24-0.99; p=0.048) were significant predictors of major complication.

CONCLUSION: Radical cystectomy with urinary diversion is associated with substantial number of complications. Patient-related (obesity) and surgeon-related (experience) factors may influence on treatment outcomes and should be considered before surgery.

FREDERIK VANDENBROUCKE

Vrije Universiteit Brussel
(Belgium)

MINIMAL INVASIVE PERCUTANEOUS TREATMENT PROCEDURES IN ONCOLOGY

Radiofrequency ablation is a minimally invasive cancer treatment used as an alternative for unresectable hepatic malignancies. Tumor ablation implies direct application of thermal or chemical therapies on a specific focal tumor. The aim of radiofrequency ablation is a total eradication of the tumor or at least a substantial tumor destruction. The thermal energy can be heat (radiofrequency, laser, microwave,...) or cold (cryoablation).

CHRISTINE DUFES

Strathclyde Institute of Pharmacy and Biomedical Sciences University of Strathclyde, Glasgow
(United Kingdom)

TUMOUR REGRESSION AFTER INTRAVENOUS ADMINISTRATION OF NOVEL TUMOUR-TARGETED NANOMEDICINE

The possibility of using genes as medicines to treat cancer is currently limited by the lack of safe and efficacious delivery systems able to deliver therapeutic genes selectively to tumours by intravenous administration, without secondary effects to healthy tissues.

We have recently demonstrated that systemically administered generation 3- polypropylenimine dendrimer combined with a therapeutic plasmid driven by a tumour-specific promoter, leads to tumour regression in murine models, with excellent long-term response. Although the expression of the therapeutic genes was tumour-specific, this gene delivery system was widely distributed in the body, which may have reduced the therapeutic potential of this system.

In order to further improve the tumour delivery capability of this system, we hypothesize that the conjugation of polypropylenimine dendrimer to the iron-carrier transferrin, whose receptors are overexpressed on numerous cancer cell lines, could result in a selective receptor-mediated gene delivery to tumours after intravenous administration and therefore lead to an increased therapeutic efficacy. Transferrin has previously been used successfully as a tumour-targeting ligand for many delivery systems.

The intravenous administration of transferrin-bearing polypropylenimine polyplex resulted in gene expression mainly in the tumours. Consequently, the intravenous administration of the delivery system complexed to a therapeutic DNA led to a rapid and sustained tumour regression over one month, with long-term survival of 100% of the animals (90% complete response, 10% partial response).The treatment was well tolerated by the animals, with no apparent signs of toxicity. Transferrin-bearing polypropylenimine is therefore a highly promising delivery system for cancer therapy.

H. SCHNECKENBURGER, P. WEBER, S. SCHICKINGER, V. RICHTER, M. WAGNER AND T. BRUNS

Hochschule Aalen, Institut für Angewandte Forschung (Germany)

VISUALIZING A CYTOSTATIC DRUG AND PROBING APOPTOSIS OF CANCER CELLS: FROM 2D TO 3D MICROSCOPY

Abstract

Methods of 2D fluorescence spectroscopy and microscopy were reported to examine the uptake, intracellular location and interaction of the chemotherapeutic drug doxorubicin in MCF-7 human breast cancer cells [1]. In particular, fluorescence lifetime appeared to be an appropriate parameter for drug response depending on incubation time as well as on the intracellular content of cholesterol. Apoptosis was further examined by a caspase sensitive membrane associated sensor based on Förster resonance energy transfer (FRET) as well as by light scattering experiments with high angular resolution.

For approaching a more realistic case which is closer to the clinical situation, 2D cell cultures were now replaced by 3D multicellular spheroids. This, however, required enhanced methods of fluorescence microscopy with high axial resolution. Low light doses needed for life cell experiments favoured the application of light sheet microscopy in comparison with laser scanning or structured illumination microscopy. Therefore, we recently adapted a light sheet module to a conventional fluorescence microscope and combined it with a microfluidic system for drug application [2]. This setup is well suitable to measure the uptake of doxorubicin with sub-cellular resolution, but reveals some problems resulting from light scattering as well as from the formation of a degradation product. Responses of various cell systems upon application of doxorubicin are presently compared.

References:

[1] P. Weber, M. Wagner, H. Schneckenburger: “Cholesterol dependent uptake and interaction of doxorubicin in MCF-7 breast cancer cells”, Int. J. Mol. Sci. 14 (2013) 8358–8366.

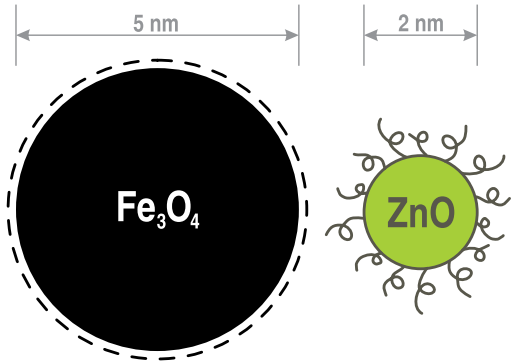
[2] T. Bruns, S. Schickinger, R. Wittig, H. Schneckenburger: “Preparation strategy and illumination of 3D cell cultures in light–sheet based fluorescence microscopy”, J. Biomed. Opt. 17(10) (2012) 101518.

SHAN-HUI HSU

Institute of Polymer Science and Engineering, National Taiwan University (Taiwan)

NANOPARTICLES FOR EFFICIENT LABELING OF HEPATOMA CELL LINE AND MESENCHYMAL STEM CELLS IN VITRO

We synthesized water-dispersible superparamagnetic iron oxide (Fe_3O_4) and fluorescent zinc oxide (ZnO) nanoparticles (NPs) for efficient cell labeling. The two water-dispersible NPs retained their imaging abilities. The cytotoxicity of Fe_3O_4 NPs (~5 nm) prepared was very low (safe until a concentration of 200 ppm). The cytotoxicity of ZnO NPs (~2 nm) prepared was higher but generally safe at the concentration of 30 ppm or below. In particular, the latter possessed good antibacterial activities. These NPs could be taken up efficiently by cells. Both cell lines (e.g. hepatoma cell line) and mesenchymal stem cells (MSCs) were successfully labeled by either type of NPs at the concentration of 25 ppm to 30 ppm. The labeled MSCs maintained their stemness marker expression and multilineage differentiation capacities. Therefore, they may be used for stem cell tracking in vivo. We are currently developing new capping agents that can not only stabilize these NPs but also carry drugs for possible therapeutic purposes.



FIORENZO VETRONE

Institut National de la Recherche Scientifique - Énergie, Matériaux et Télécommunications, niversité du Québec, Varennes
(Canada)

UPCONVERTING NANOPARTICLES FOR IMAGING, DIAGNOSTIC AND TREATMENT OF CANCER

Multiphoton excited luminescent nanomaterials are emerging as useful tools in diagnostic medicine and therapeutics. These nanomaterials are excited with near-infrared (NIR) light mitigating some of the drawbacks associated with the use of UV light as the excitation source. NIR light is silent to tissues thus minimizing autofluorescence, possesses greater tissue penetration capabilities and does not incur damage to the sample. However, these nanomaterials require femtosecond (fs) excitation light to induce the multiphoton excited luminescence.

It is in this regard that there has been an ever-increasing interest in lanthanide (Ln3+)-doped upconverting nanoparticles (UCNPs) as an alternative to more common multiphoton excited nanomaterials. With UCNPs, it is possible to obtain UV/visible/NIR emissions using a single NIR excitation source (typically 980 nm) via a process known as upconversion. This multiphoton excitation process, differs from what occurs in conventional multiphoton excited materials where the absorption of photons is simultaneous. In the case of Ln3+-doped materials, the multitude of long-lived “real” electronic energy states of the Ln3+ ions (from the partially filled 4f shell) allow for sequential absorption of multiple NIR photons eliminating the need for complex and expensive optical excitation. Thus, upconverted luminescence can be observed using an inexpensive commercial continuous wave diode laser.

Here, we present the synthesis of Ln3+-doped UCNPs and demonstrate how they can be used in biological applications. However, before these biological studies can be performed, the surface of the UCNPs must be modified, first to impart water dispersibility and second to attach chemically and/or biologically relevant molecules. Furthermore, we will show how these UCNPs can be used as building blocks towards developing a multifunctional nanoplatform for the potential diagnostics and therapeutics of diseases such as cancer.

Keywords: lanthanides, upconversion, luminescence, fluorescence imaging

NILS CORDES

OncoRay – National Center for Radiation Research in Oncology, and Dept. of Radiotherapy and Radiation Oncology, University Clinic, Medical Faculty Carl Gustav Carus, Dresden University of Technology
(Germany)

3D ECM BASED CELL CULTURE MODELS FOR STUDYING CELLULAR RESISTANCE TO IONIZING RADIATION

Lack of translation of in vitro results into the clinic remains dramatically unchanged. Unaltered cancer death rates and parallel constantly increasing funding volumes over the past 50 years seem not to be strong enough stimulators for reconsideration of our research strategies. Over 30 years of intense investigations can be surveyed for key studies providing evidence that ex vivo culture of cells under two-dimensional (2D) monolayer conditions cause up to 90% loss of the original in vivo phenotype. Similar to gene expression, normal and cancer cells exhibit altered proteome and phosphoproteome, protein-protein interactions, signal transduction, and response to external stimuli or cytotoxic agents as used in medicine today. Based on the absence of a feasible 3D extracellular matrix (ECM) based cell culture model for exploring therapy efficacy, we have established a robust laminin-rich (lr) ECM cell culture model in which all state-of-the-art molecular and cell biology techniques can be performed. Focusing mainly on cancer, we were able to demonstrate the usefulness of this model for cancer research by evidently showing for various relevant endpoints that our lrECM approach reflects in vivo cell behavior and radiation and drug response. In this overview lecture, I will illustrate how this model works, what the evidence is, and set all these aspects in the context of modern cancer therapy with particular recognition of radiotherapy.

ARUN KUMAR

Nanomedicine Research Laboratory, Department of Medical Laboratory Science, College of Health Sciences, University of Delaware
(USA)

CELL-MEDIATED NANO ENCAPSULATED DRUG FOR TARGETED DELIVERY INTO LUNG

Using current methodologies, drug delivery to small airways, terminal bronchioles, and alveoli (deep lung) is inefficient, especially to the lower lungs. Urgent lung pathologies such as acute respiratory distress syndrome (ARDS) and post-lung transplantation complications are difficult to treat, in part due to the methodological limitations in targeting the deep lung with high efficiency drug distribution to the site of pathology. To overcome drug delivery limitations inhibiting the optimization of deep lung therapy, isolated rat Sertoli cells preloaded with chitosan nanoparticles were use to obtain a high-density distribution and concentration (92%) of the nanoparticles in the lungs of mice by way of the peripheral venous vasculature rather than the more commonly used pulmonary route. Additionally, Sertoli cells were preloaded with chitosan nanoparticles coupled with the anti-inflammatory compound curcumin and then injected intravenously into control or experimental mice with deep lung inflammation. By 24 h postinjection, most of the curcumin load (~90%) delivered in the injected Sertoli cells was present and distributed throughout the lungs, including the perialveloar sac area in the lower lungs. This was based on the high-density, positive quantification of both nanoparticles and curcumin in the lungs. There was a marked positive therapeutic effect achieved 24 h following curcumin treatment delivered by this Sertoli cell nanoparticle protocol (SNAP). Results identify a novel and efficient protocol for targeted delivery of drugs to the deep lung mediated by extratesticular Sertoli cells. Utilization of SNAP delivery may optimize drug therapy for conditions such as ARDS, status asthmaticus, pulmonary hypertension, lung cancer, and complications following lung transplantation where the use of high concentrations of anti-inflammatory drugs is desirable, but often limited by risks of systemic drug toxicity.

L. KELBAUSKAS, J. ZENG, S. ASHILI, B. UEBERROTH, K. LEE, M. RODRIGUEZ, G. KIM, V. NANDAKUMAR, C. READING, N. ANSEN, P. SENECHAL, W. GAO, B. ASHCROFT, T. TRAN, T. Y. TIAN, R. JOHNSON, AND D. MELDRUM

Center for Biosignatures Discovery Automation, Biodesign Institute, Arizona State University, Tempe.
(USA)

T. PAULSON, B. REID

Fred Hutchinson Cancer Research Institute, Seattle.
(USA)

INTEGRATED MULTIPARAMETER SINGLE-CELL ANALYSIS OF METABOLIC PHENOTYPE, GENE TRANSCRIPTION LEVELS AND NUCLEAR ARCHITECTURE IN PREMALIGNANT PROGRESSION OF BARRETT'S ESOPHAGUS

Intercellular heterogeneity is an emerging theme in cell biology research that is increasingly recognized as pivotal in a variety of vital processes in vivo. Cell-to-cell differences play a central role in responses to microenvironmental alterations, and at the onset of many diseases including cancer. Barrett's esophagus (BE) is a pre-malignant condition that predisposes to esophageal adenocarcinoma (EAC), a highly lethal form of cancer with a rapidly increasing incidence rate in the western world. Because of its accessibility to biopsies, BE represents a unique model system for studying pre-malignant to malignant progression and associated alterations at the histological, cellular, intracellular, and biomolecular level.

We present a single-cell level study on phenotypic, gene transcription and nuclear architecture alterations associated with pre-malignant to malignant progression in BE. Using a suite of new technologies developed by our group we investigated how alterations in gene transcription levels at different stages of progression affect the metabolic phenotype and nuclear architecture in individual cells. We observe marked changes in population-level cellular heterogeneity with regard to metabolic rates, expression levels of genes involved in several key pathways associated with carcinogenesis, and chromatin organization. We find early manifestation of the cancerous phenotype in dysplastic cells and that mitochondria play a significant role in hypoxia adaptation of BE cells. We show potential evidence of clonal evolution in cancer based on changes in metabolic rate heterogeneity in response to selective pressure conferred by hypoxia.

UNA RIEKSTINA

Department of Pharmacy, Faculty of Medicine, University of Latvia (Latvia)

MESENCHYMAL STEM CELL THERAPY BIOSAFETY ISSUES

Stem cells are a new class of therapeutics that has the ability to regenerate the damaged organs or tissues in the body to restore its normal functions. Stem cell-based treatment of cardiovascular diseases, musculoskeletal disorders, cancer, macular degeneration, autoimmune disorders, and graft versus host disease currently are in phase II/III clinical trials[1].

Mesenchymal stem cells (MSCs) are found in the stroma of many organs. MSCs are defined as plastic adherent cells with spindle like morphology, that express CD73, CD90, and CD105 surface markers and have tri-lineage differentiation potential[2, 3]. MSCs possess immunomodulatory properties and home to the sites of inflammation and tumour. Therefore MSCs are promising candidates for the cell-based anti-cancer therapies[4]. Despite of the great therapeutic potential, there are biosafety risks associated with the stem cell use, mainly immunogenicity and malignant transformation[5]. Establishment of biosafety criteria is essential for stem cells clinical applications. In our study we have addressed two issues:
1) characterization of MSC differentiation using Fourier transforming infrared (FT-IR) spectroscopy; 2) analysis of proliferation marker Ki-67 and telomerase reverse transcriptase TERT expression in MSCs to monitor tumorigenicity during *in vitro* propagation.

Our results clearly demonstrate that FT-IR spectroscopy detected qualitative and quantitative changes in different macromolecular fractions - lipids, proteins and carbohydrates during MSC neurodifferentiation. Thus, FT-IR spectroscopy approach allows fast examination of the stem cell differentiation status.

Our preliminary data suggest that there is correlation between the Ki-67 and TERT expression level and cell tumorigenicity. Ki-67 and TERT biomarker screening might be considered as a useful tool to monitor tumorigenicity risk during *in vitro* MSC propagation.

Key words: mesenchymal stem cells, biosafety, tumorigenicity, FT-IR

1. Medicines in development Biologicals PhRMA report 2013, www.phrma.org
2. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy.2006;8(4):315-7.
3. Riekstina U, Cakstina I, Parfejevs V, et al. Embryonic stem cell marker expression pattern in human mesenchymal stem cells derived from bone marrow, adipose tissue, heart and dermis. Stem Cell Rev. 2009;5(4):378-86.
4. Tang C, Russell PJ, Martiniello-Wilks R, et al. Concise review: Nanoparticles and cellular carriers-allies in cancer imaging and cellular gene therapy? Stem Cells. 2010;28(9):1686-702.
5. Barkholt L, Flory E, Jekerle V, et al. Risk of tumorigenicity in mesenchymal stromal cell-based therapies-Bridging scientific observations and regulatory viewpoints. Cytotherapy. 2013;15(7):753-9.