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Paraneoplastic Neurological Syndromes

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Paraneoplastic neurological syndromes (PNS) are rare, but very disabling disorders. The most common PNS include − paraneoplastic encephalomyelitis (often in combination with neuropathy), paraneoplastic cerebellar degeneration, opsoclonus-myoclonus, stiff-person syndrome, visual paraneoplastic syndromes, peripheral neuropathy and disorders of the neuromuscular junction. They arise as remote effects of several different types of tumours, most frequently small cell lung cancer, breast cancer, gynaecological tumours, and lymphoma. PNS occur in approximately 1% of cases with such tumours. Onconeural antibodies represent an important shortcut to the diagnosis of PNS and the detection of such antibodies often directs the search of the underlying tumour. These antibodies may also be of pathogenic importance as they target critical functional epitopes that are linked to apoptotic neuronal death. However, cytotoxic T lymphocytes probably play a major or complementary pathogenic role. It is important to identify PNS for the following reasons: 1) PNS may involve any part of central and/or peripheral nervous system and may mimic other neurological complications of cancer such as metabolic deficits, coagulopathy, infection and the side effects of therapy; 2) In 60%−70% of patients, the PNS develops before the tumour is manifest. Recognition of the paraneoplastic disorder may, therefore, lead to early diagnosis of the tumour with potential for better treatment-response of both the underlying tumour and the paraneoplastic syndrome.

Society Session (Sun, 25 Sep, 16:45−18:15) **European Society of Oncology Pharmacy (ESOP)**

241 INVITED

Absorption Issues With Oral Drugs

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Drug substances have to reach their place of action within the body in the appropriate concentration for a defined time span in order to be effective and safe. This prerequisite holds true for every kind of delivery system and route of administration. Among the different routes of administration the oral route is by far the most common way for the administration for pharmacologically active substances. For a long time this did not hold true for chemotherapy of cancer. However, in the meantime oral administration of anticancer drugs is increasing. Oral drug administration is very convenient. As the gastrointestinal tract is the natural site for the uptake of all essential substances with exception of oxygen it is also often regarded as a rather simple organ where food (and drug) absorption occurs by passive diffusion. In contrast, the gastrointestinal processing of food is a very complex process that is managed by the “second brain” of the body, the so-called “gut brain”. As a consequence the delivery of drug substances via the oral route is often much more challenging than other routes of administration as for example the direct delivery into the body via injection or infusion. The complexity of oral drug absorption is also reflected by the fact that despite numerous attempts until today a reliable prediction of the rate and extent of the absorption of drug substances from the human gastrointestinal tract is neither provided by in silico methods nor animal models. Variability in oral drug absorption can be a result of variable transit times through the different parts of the gastrointestinal tract. Improtant parameters that are influencing transit times and absorption conditions are for example the relation between the administration of the dosage form and food intake, fluid intake as well as properties of the delivery system like size and density. Consequences resulting from the interplay between substance properties, gastrointestinal physiology and drug delivery technology will be demonstrated by means of some examples. Data on gastric residence, small intestinal transit and colon transport will be presented and discussed. Special focus will be given to food induced mechanisms like gastric retention, gastro-colonic and gastro-ileocecal reflexes.

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Adherence Issues With Oral Chemotherapy

M. Daouphars[1]. [1]*Cancer Centre Henri Becquerel, Pharmacy, Rouen, France*

A growing proportion of anticancer treatments presents as oral chemotherapy. These offer patients many potential advantages as ease of administration, and fewer trips to the hospital. However oral chemotherapy is effective only if patients adhere to their administration schedule. While patients prefer the convenience of oral medications, there is some concern with regard to patients' adherence with therapy as non-adherence is prevalent in half of patients in the general population. Although it may be assumed that cancer patients would be more adherent due to the gravity of their disease, the few studies available report significant non-adherence rates. Even if clear data are lacking on consequences of non-adherence in cancer patients, non-responsiveness, unnecessary diagnostic testing, changes in dose or therapeutic regimen, and hospitalizations may be expected. Adherence to treatment depends on many co-existing factors, including patient factors, treatment regimen and interactions with healthcare system. Care givers are to be aware of these adherence issues in order to identify potential non-adherent patients, and to propose patients education programs, as there is some evidence that interventions to encourage the accurate self-administration of oral therapies can be effective.

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Pharmacist Role

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Antineoplastic chemotherapy describes a group of hazardous drugs commonly used in the treatment of cancer.
Potential risks are not only recognized for patients being treated, but extend to pharmacists and other health care workers who handle the drugs
– Adverse reproductive outcomes such as miscarriages, birth defects, fetal loss, infertility
– Acute symptoms such as irritation, sore throat, cough, dizziness, headache, allergic reaction, diarrhea, nausea and vomiting.

Because of the safety issues, guidelines for safe handling are well established in the traditional settings of hospitals and ambulatory clinics for the intravenous chemotherapy in traditional oncology settings.
In tumour therapy, documentation, quality management and standardisation of interdisciplinary processes are increasingly gaining importance in form of therapy protocols and guidelines for clinical treatment.
Non-adherence, application errors and interactions due to insufficient education of the patient can compromise therapeutic success. An adequate, quality assured, multi-professional care is therefore urgently required for oncology patients receiving oral chemotherapy.
A Pilot program is set up in Germany to teach 20,000 community and hospital pharmacist in supporting patients the best in taking oral cytotoxic drugs.
Through the action of pharmacists the collaboration of physicians, project- and industrial partners the initiative aims to reach the following goals for oncology patients:

1. On-site optimisation of oral chemotherapy and improvement of pharmaceutical care for oncology patients
2. Cost-effective and reliable care for cancer patients due to professional collaboration of local physicians, pharmacists and other health care professionals at the right time
3. Recognising and solving drug related problems related to oral chemotherapy
4. Enhancing the quality of life of oncology patients through a coordinated management of side effects and interactions during and after therapy
5. Providing new insight as a contribution to health services research and to encourage drug safety.

Society Session (Sun, 25 Sep, 16:45−18:15) **European School of Oncology (ESO) − Prostate Cancer Units**

244 INVITED

Prostate Cancer Patients − What do They Really Need?

L. Denis[1], E. Briers[2], F. Boeye[3], H. Van Daele[3], B. Dourcy-Belle-Rose[2], A. Costa[4]. [1]*Europa Uomo, Secretary, Antwerp,* [2]*Europa Uomo, Europa Uomo, Antwerp,* [3]*Oncology Centre Antwerp, OCA, Antwerp, Belgium;* [4]*Europa Uomo, Europa Uomo, Milan, Italy*

Facing the diagnosis of cancer remains a challenge for most if not all unprepared men.
No matter how well informed by his treating physician, with the inclusion of the routine patient brochures, the first reactions include disappointment and anxiety, hidden from his beloved ones and his physician.
Even informed on the relative benign course of prostate cancer they panic with the thought of impotence and incontinence for the rest of their life. They all claim to prefer to know the truth but at the same time they need professional and caring support to face the same truth.
A number of factors complicate this support.
Most important is to secure practical, relevant, updated, correct information on their specific situation in the preventive and clinical course of the disease

that is easy to understand and permanently available. It is evident that this information is evidence based if possible, usually conventional wisdom and always conscious based searching for optimal medical treatment. Europa Uomo expects and does receive this information, yearly updated, from our scientific committee.
Next to this highway of high quality information we see patient-centered care as our domain where we welcome professional help but want to be involved from the start on any project or progress in patient care be it psychological, social, financial or involving quality of life and/or health economics.
Entering the labyrinth of medical care requires consistent quality aid and specific objective guidance to follow a care path in our social health care system. We claim patient rights but also patient obligations.
The choice of your treating specialist or rather the treating multiprofessional team is a first step to a better outcome of treatment.
The net results of the many uncertainties in the dialogue to a shared decision on primary treatment are stress and anxiety leading to fatigue and psychiatric treatment. Determining the individual disease treatment and the outcomes that matter to each patient are essential to reach the expected health related quality of life (HRQoL). Next to cure or control of the cancer patients worry most of the side-effects of treatment and the impact on their lifestyle as well as on the lifestyle of their partner. We hope to see the publication of outcomes of all procedures and treatments in an updated database which is easier to understand then sophisticated statistics, p-values and confidence intervals.

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The Concept of Prostate Cancer Units

R. Valdagni[1], L. Bellardita[1], C. Parker[2], C.N. Sternberg[3], B. Tombal[4], L. Denis[5], A. Costa[6]. *[1]Fondazione IRCCS Istituto Nazionale Tumori, Prostate Program, Milan, Italy; [2]The Royal Marsden NHS Foundation Trust, Academic Urology Unit, Sutton, United Kingdom; [3]San Camillo and Forlanini Hospitals, Department of Medical Oncology, Rome, Italy; [4]Cliniques Universitaires Saint-Luc, Department of Urology, Brussels, [5]Europa Uomo Europa, Antwerp, Belgium; [6]European School of Oncology, Milan, Italy*

Background: In prostate cancer (PC) multiple treatment/observational options are available. Multidisciplinary (MD), multiprofessional management facilitates high-quality medical procedures, collaboration among dedicated specialists, preventing and managing physical and emotional disease- or treatment-induced complications.
Materials: Following the experience with breast cancer, in 2010 the European School of Oncology promoted the identification of general recommendations as well as mandatory requirements for the set up of PCU in a discussion paper. A PCU should be referred $\geqslant$100 newly diagnosed PC cases each year. Therapeutic/observational protocols should be carried out under the direction of PCU. Data should be recorded and available for audit once a year. A PCU should have a core team trained in PC who dedicates an agreed time to PCU and attends MD meetings (MDM): PCU Clinical Director, $\geqslant$1 uro-pathologists, $\geqslant$2 urologists, $\geqslant$2 radiation oncologists, $\geqslant$1 medical oncologists, 1 nurse specialist in PC, $\geqslant$1 data managers, 1 professional responsible for the compilation of patient data. The PCU should have access to associated services and non-core personnel: $\geqslant$1 radiologists, $\geqslant$1 medical physicists, $\geqslant$2 radiation therapy technologists, $\geqslant$1 physiotherapists, $\geqslant$1 palliative care specialists, 1 clinical psychologist, 1 sexologist/andrologist, 1 geriatrician, $\geqslant$1 clinical trial coordinators, patient advocates.
One urologist, one radiation oncologists and one medical oncologist (if possible and whenever indicated, a psychologist) should participate synchronously or in rapid succession in a weekly MD clinic. Advanced, recurrent or metastatic PC patients (pts) should be offered clinic every 2 weeks. Follow up should be supervised by PCU core members. All options should be offered and the pt's right to information and self-determination ensured.
In weekly MDM min 90% PC cases should be discussed and decisions documented in charts.
PCU should possess or have access to all the technological equipment for imaging, radiotherapy, pathology.
Conclusions: The set up of PCU requires to reorganize services, workflow and attitudes but it should have a favorable economic impact and avoid multiple consultations and inappropriate treatments. PCU certification should be considered the necessary step forward to ensure optimal treatment and care. The aim of this symposium is to start discussing about the set up of PCU in Europe.

References

Valdagni et al *Eur J Cancer* 47, 2011
Gomella et al *JOP* 6, 2010
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Monday 26 September 2011

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) How to Understand and to Reverse Drug Resistance in Metastatic Breast Cancer

246 INVITED

Functional Genomic Approaches to the Dissection of Cancer Drug Resistance Mechanisms

C. Swanton[1]. *[1]CR-UK London Research Institute, Translational Cancer Therapeutics Laboratory, London, United Kingdom*

Drug resistance contributes to early treatment failure and deteriorating quality of life for patients with cancer. Deriving gene expression based predictors of drug sensitivity from microarray data is an associative learning process that is inherently vulnerable to the over-fitting of data. Such statistical considerations may require new approaches to the discovery of predictive biomarkers of drug response. Functional genomics screening approaches using RNA interference technologies have begun to dissect drug sensitivity pathways, revealing molecular mechanisms that may influence response to endocrine, cytotoxic and targeted therapeutic approaches in the clinical setting. Results from such functional genomics-driven biomarker discovery strategies and potential caveats in the search for novel predictive biomarkers will be discussed.

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PARP Inhibitors Sensitivity and Resistance

T. Helleday[1]. *[1]University of Oxford, Radiation Oncology and Biology, PRI Churchill Hospital Headington, Oxford, United Kingdom*

Inherited mutations in either the *BRCA1* or *BRCA2* genes provide an increased risk for breast cancer. Cancers defective in either of the *BRCA* genes also have a defect in homologous recombination (HR), which will increase the genetic instability in the cancers and drive disease progression. Previously, we and others identified that *BRCA* mutated tumours are highly sensitive to inhibitors of the DNA repair enzyme Poly(ADP-ribose) polymerase (PARP). Interestingly, PARP inhibitors are only toxic in the *BRCA* mutated cells and hence there is a synthetic lethal relation between PARP and BRCA. The underlying mechanism for the PARP-BRCA synthetic lethality was initially attributed to accumulation of DNA strand breaks after PARP inhibition that required BRCA-mediated HR for repair. Here, I will provide evidence that this simple explanation is incomplete and that other complex underlying mechanism are also relevant. Importantly, some *BRCA* mutated cancers fail to respond to PARP inhibitors in clinical trials and many responding *BRCA* cancers eventually develop resistance to PARP inhibitors. Here, different mechanisms for PARP inhibitor resistance are discussed. Furthermore, novel strategies to overcome PARP inhibitor resistance are presented.

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How to Reverse the Resistance to Trastuzumab

F. Andre[1], M. Campone[2]. *[1]Institut Gustave Roussy, Department of Medical Oncology, Villejuif, [2]Centre Gauducheau, Department of Medical Oncology, Nantes, France*

Several preclinical studies have suggested that activation of mTOR pathway, through PTEN loss and PIK3CA mutations, could mediate resistance to trastuzumab. Based on this background, a clinical research program has been launched to adress the hypothesis that mTOR inhibitors could reverse resistance to trastuzumab.
Phase I trials have allowed detecting first signals for efficacy and finding the doses for further studies. In the phase I trials combining paclitaxel, trastuzumab and everolimus (mTORC1 inhibitor), 44% of the patients have presented an objective response. This phase I study proposed a 10 mg daily schedule for further development. In the phase I trial combining vinorelbine, trastuzumab and everolimus, the response rate was 19% and the 5 mg daily dosage for everolimus was selected for further studies. Two phase II trials have been done, that confirmed that mTOR inhibitors reverse resistance to trastuzumab. In the phase II trial developed by MD Anderson, patients were selected to present a resistance to trastuzumab, and were treated with trastuzumab and mTOR inhibitors, without any cytotoxic agents. In this study, the response rate was 13%. Based on the results of these phase I/II trials, two randomized trials have been started. In addition to clinical development, several teams are developing biomarker programs in order to better identify which patients should be proposed a mTOR inhibitor.