

Epidermal growth factor receptor mutations and treatment of non-small-cell lung cancer

Tanja Čufer, Tanja Ovčariček and Izidor Kern

The 5-year relative survival rates of patients with lung cancer are approximately 12%, and have increased only by 2.2% during the last 15 years. Third generation chemotherapy based on platinum derivatives is currently a standard treatment for the advanced non-small-cell lung cancer (NSCLC) but has probably reached a plateau. With the advent of targeted therapy it has been introduced into the clinical management of advanced NSCLC as well. Epidermal growth factor (EGFR) is a transmembrane glycoprotein which is expressed on the cell surface of a tumor as well as on normal cells. It belongs to the ErbB receptor family, which includes four types of receptors. In the article only EGFR (HER1/ErbB1) will be considered. Treatment with two small molecules, tyrosine kinase inhibitors (TKIs) directed against the epidermal growth factor receptor (EGFR), namely gefitinib and erlotinib, already proved to be an effective treatment strategy in patients with advanced NSCLC. Among different methods used for EGFR status determination, only identification of activating

mutations in the EGFR gene domain proved to be a very reliable and significant predictor for the response to EGFR-directed TKIs therapy in NSCLC. Even though the activating EGFR mutations were found to be more frequent in patients with particular clinico-pathological characteristics, such as females, non-smokers, those with adenocarcinoma histology, a selection of patients based on these characteristics does not allow for a proper selection of patients for EGFR-directed TKI therapy. Only by determining the activating EGFR mutations in the primary tumor can the identification of NSCLC patients with expected high response rates to EGFR-directed TKI therapy leading to long survival and a good quality of life be achieved. Personalized medicine for NSCLC patients is now reality, and EGFR mutation status should be determined in the primary tumor of all patients prior to any systemic therapy for advanced disease, thus allowing us a tailored first-line and subsequent lines of systemic therapy in each individual patient.

Ultrasound-guided fine needle aspiration biopsy of renal tumors

Margareta Strojjan Fležar, Bojana Černelč, Helena Gutnik and Alenka Višnar Perovič

In Slovenia the ultrasound-guided fine needle aspiration biopsy is a standard diagnostic procedure for assessment of renal tumors with non-characteristic radiologic features. Over the past year the interest in this method has been increasing across Europe, especially for the evaluation of small renal masses, defined as smaller than or equal to 3 cm. Our analy-

sis confirmed that the method is reliable for the assessment of small renal masses, provided that cellular material is sufficient and representative for the lesion. Adjunct methods like immunocytochemical stainings can improve typing of renal cell carcinomas: clear cell, papillary and chromophobe type.

Inflammatory breast cancer – recommendations for diagnosis and treatment

Cvetka Grašič Kuhar, Kristijana Hertl, Barbara Gazić, Elga Majdič and Janez Žgajnar

Inflammatory breast cancer (IBC) represents 1-5% of all breast cancer. Early and accurate diagnosis of this aggressive disease is of critical importance for the outcome. Diagnosis is made based upon its typical clinical appearance (breast erythema, edema and/or peau d'orange) and histopathological confirmation of invasive cancer. A multimodality approach is recommended for treatment. The initial treatment recommended in a localised disease is primary systemic chemotherapy with anthracyclines and taxanes for a duration of 4-6 months. The surgical treatment of choice is a modified radical

mastectomy, followed by adjuvant radiation of the mammary region and ipsilateral supraclavicular region. According to predictive factors, adjuvant hormonal and/or trastuzumab therapy is indicated; the latter could be used in combination with taxanes even in the neoadjuvant setting. Despite the multimodality approach, the outcome of IBC is not optimal (median overall survival in localised disease patients is less than four years). Patients with IBC should be treated in experienced oncological centres with the possibility of cooperation in international randomised clinical studies.

S100B – Tumor marker in cutaneous melanoma

Barbara Perić, Ivana Žagar, Srdjan Novaković, Janez Žgajnar and Marko Hočevar

Introduction. An increased level of serum S100B can serve as a marker of metastatic spread in patients with cutaneous melanoma (CM). In patients with elevated S100 B and/or clinical signs of disease progression, a PET-CT scan is a valuable tool for discovering metastases and planning treatment. The aims of this study were to determine whether regular measurements of serum S100B are a useful tool for identifying patients with CM metastases and for evaluating the diagnostic value of PET-CT during the follow-up.

Methods. From September 2007 to February 2010, 115 CM patients included in regular follow up at the Institute of Oncology Ljubljana were appointed to receive PET-CT scans. They included 82 (71.3%) patients with clinical signs of disease progression and 33 (28.7%) asymptomatic patients with two subsequent elevated values of S100B. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) of S100B and PET-CT were calculated using standard procedures.

Results. Disease progression was confirmed in 81.7% of the patients (in 86.5% of patients with clinical signs of disease

progression and in 69.7% of asymptomatic patients with elevated S100B). Sensitivity, specificity, PPV and NPV of S100B was 33.8%, 90.9%, 96.0% and 17.5%, respectively, in patients with clinical signs of disease progression. For 20.0% of the patients increased serum S100B was the only sign of disease progression. Sensitivity and PPV of S100 in this group of patients were 100.0% and 69.7%, respectively.

PET-CT disease progression was diagnosed in 84.2% of symptomatic patients and in 72.7% of asymptomatic patients with elevated S100B. The sensitivity, specificity, PPV and NPV of PET-CT for symptomatic patients was 98.5%, 90.9%, 98.5% and 90.9%, respectively, and 100%, 90.0%, 95.8% and 100%, respectively, for asymptomatic patients with elevated S100.

Conclusions. Measurements of serum S100B during regular follow-up of patients with CM are a useful tool for discovering disease progression in asymptomatic patients. The value of its use increases if measurements are followed by extended whole body PET-CT.

Addison's disease in patients with an unidentified panhypopituitary condition following observed atypical meningioma (primary description)

Tomaž Kocjan, Lorna Zadavec Zaletel and Berta Jereb

Radiotherapy is a proven and successful way of treating brain tumors. One should be aware, however, of its acute side effects as well as late consequences, often only apparent years after concluded treatment. The endocrine glands, primarily the hypothalamus and pituitary gland, are the most common-

ly affected organs. We present a clinical case to illustrate that, after irradiation of the head, patients should have periodic endocrinological testing and adequate hormonal substitution, when necessary.

Use of the HPV DNA test for cervical cancer screening

Matejka Rebolj

An infection with oncogenic types of Human Papillomavirus (HPV) is a necessary condition for development of cervical cancer. The incidence of cervical cancer has decreased over the years in line with the use of cytology screening. Nevertheless, cytology is not an optimally sensitive screening test for cervical intraepithelial neoplasia (CIN), and a more sensitive test would be beneficial. The aim of this paper was to describe the characteristics of HPV DNA tests as observed

in all eight randomized controlled trials with published data that compared HPV tests and cytology in primary screening. These trials showed that the sensitivity of HPV tests for \geq CIN3 is higher than the sensitivity of cytology. In several trials, the higher sensitivity in the baseline screening rounds led to fewer diagnoses of cervical cancer by the subsequent screening round than was the case with cytology, although these observations were based on few cases per trial. It will

be a greater challenge to limit the amount of extra unwanted side effects of HPV testing compared with cytology. These are predominantly false-positive tests, i.e. positive screening tests without a subsequent diagnosis of \geq CIN3, and extra diagnoses of CIN grades with a low probability of progression to cervical cancer, i.e. CIN1 and to some degree also CIN2. The three most widely discussed approaches to reducing

the burden of the extra unwanted effects were discussed in this paper: the use of triage tests in women with positive HPV screening tests, the use of HPV tests from the age of 30 years onwards only, and a change in the threshold value for a positive HPV test. Each of these approaches is associated with distinct advantages and disadvantages.

Circulation of tumor cells and their effect on breast cancer – reviewing the results of previous studies

Tanja Marinko, Tamara Lah Turnšek and Gregor Serša

Circulating tumor cells (CTCs) are epithelial tumor cells detected in the peripheral blood of patients with solid malignant tumors. They originate from the primary tumor or metastatic sites. New techniques have been developed to isolate and characterise these cells, including the FDA-approved Cell-Search, which are using mainly cytometric/antibody-based and molecular approaches. Recent advances in theories regarding metastasis support the role of early release of tumor cells in the neoplastic process. It has been found that

phenotypic variation exists between the primary tumor and CTCs. Of particular interest is the difference found between primary tumor and CTC HER-2 status in both metastatic and early breast cancer. CTC enumeration has been incorporated into different fields of oncology as a prognostic marker, a tool to monitor therapy response, and a method to understand basic tumor characteristics. But currently, there is still no role for CTCs in clinical practice.

Distribution of human papillomavirus genotypes in women with cervical cancer and cervical intraepithelial neoplasia grade three (CIN 3) in Slovenia

Nina Jančar, Eda Vrtačnik Bokal and Mario Poljak

Cervical cancer (CC) evolves through several stages of precancerous lesions and can therefore be prevented by means of a screening program; if detected at an early stage it can also be efficiently treated. Sexually transmitted infection with oncogenic human papillomavirus (HPV) genotypes has been confirmed to be a single necessary etiological factor for the development of cervical precancerous lesions and CC. In order to assess the potential local benefit of prophylactic HPV vaccination, we established the distribution of HPV genotypes in a representative sample of women with CC and high grade cervical intraepithelial lesions (CIN 3) in Slovenia.

HPV DNA was found in 262/278 CC samples (94.2%). HPV 16, HPV 18 and HPV 33 were the HPV genotypes most frequently found in CC samples in Slovenia. HPV DNA was found in 253/261 samples of CIN 3 (96.9%). In 80.6% of the samples infection with a single HPV genotype was found, whereas in other samples more than one HPV genotype was found (2 to 9 HPV genotypes). Prophylactic HPV vaccination with currently available vaccines could theoretically prevent up to 77% of cases of CC and up to 60% of cases of CIN 3 caused by HPV 16 and HPV 18 in Slovenia.

Neuroendocrine tumors originating in the gastrointestinal tract

Maja Ebert Moltara and Janja Ocvirk

Neuroendocrine tumors (NET) belong to the group of rare tumors, though their incidence is increasing. Diagnosis and treatment vary among groups of different primary origins. NETs of gastrointestinal origin (GEP-NET) are slow growing tumors; however, most patients with GEP-NET are not diagnosed until the metastatic spread of the disease has already occurred. Somatostatin analogues are the mainstream treatments of symptom and tumor growth control in these patients. Other systemic therapies depend on the biologic potential of the tumor.

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Alleviating symptomatic heavy breathing in terminal patients

Mirjana Rajer

Dyspnoea is a distressing symptom frequently present in patients with incurable diseases. The goal of treatment for patients in the terminal stage is symptom control. Unfortunately, optimal treatment of dyspnoea has not been achieved in all patients yet. Frequent mistakes include unnecessary diagnostic procedures and suboptimal symptom control. In

this review, the definition of dyspnoea is presented, followed by etiologic and epidemiologic data and pharmacological and non-pharmacological measures for relief. At the end, two more symptoms are presented; terminal rattle and massive pulmonary haemorrhagia.

Side effects of radiotherapy on the brain

Matija Zupan and Tanja Roš Opaškar

There are numerous and often unpredictable side effects of radiotherapy on the brain. The damage can be direct or indirect, and becomes apparent acutely or even many years thereafter. The distinction between these forms is important since early side effects are predominantly reversible whereas late ones usually are not. The incidence of radiotherapy-induced side effects is hard to estimate due to the differing definitions and methodologies used in clinical studies. Nevertheless, the clinical picture often resembles the progression of pre-existent malignant disease. The mechanism underlying side effects of radiotherapy is mainly injury to glial cells and cerebral endothelial cells. The hippocampus is especially prone to radiation damage. The burden of radiation damage in a given individual is dependent upon many factors. Concomitant systemic and intrathecal chemotherapy adds significantly to neurotoxicity. Diagnosing side effects of

radiotherapy can be a daunting task since the time interval between radiotherapy and the occurrence of neurological side effects is variable. What is more, the clinical picture can resemble metastatic, paraneoplastic or other neurological disease. It is therefore of crucial importance to be aware of the fact that the clinical picture can be ascribed to side effects of radiotherapy only after other possible reasons (mainly tumor progression) have been effectively ruled out. The article entails a broad spectrum of direct and indirect radiotherapy-induced consequences on the brain. Acute encephalopathy is connected to blood-brain barrier disruption. Early-delayed encephalopathy is caused by demyelination. Late-delayed encephalopathy is represented mainly by radiation necrosis. Cognitive decline as a consequence of radiotherapy is still a matter of hot debate.

The informatization of patient treatment with antitumor drugs

Monika Sonc

Effective IT support is a requirement for the quality treatment of patients by allowing control over the management of their treatment and by facilitating the work of the medical professionals. At the Institute of Oncology Ljubljana utilisation of drugs is supported by a computer program that enables a holistic approach to treatment with anticancer drugs as well

as the preparation of these medicines. The program combines various aspects of such treatment and the preparation of medicines, and it enables an interdisciplinary team of health professionals to optimize the quality, safety and economy of treatment with antitumor drugs.

Clinical development of new systemic therapies in patients with metastatic prostate cancer

Boštjan Šeruga, Tomaž Milanec, Simona Borštnar, Nataša Snoj Šarvari and Breda Škrbinc

Hormonal therapy with castration is initially effective in the majority of men with metastatic prostate cancer, but the disease invariably progresses. Docetaxel in combination with prednisone is the standard first-line treatment in men with metastatic castration-resistant prostate cancer (mCRPC). Although several experimental agents have been evaluated in

combination with docetaxel to date, none of these combinations improved the efficacy of docetaxel. Cabazitaxel and abirateron acetate are new options for systemic treatment in men with mCRPC who have progressive disease after treatment with docetaxel.