736

Molecular concepts

R. Stahel. *Universitatsspital Zurich, Department of Oncology, Zurich, Switzerland*

Much has been learned about the molecular changes and importance of signal transduction pathways in lung cancer over the last decades. There is great hope that therapeutic interventions aiming at specific molecular pathways might overcome the impasse of therapeutic advances seen with systemic chemotherapy and that molecular properties of tumors with prognostic and predictive significance might lead to new therapeutic approaches. The first clinical studies on targeted therapy involved the substitution of inactivated tumor suppressor genes by viral transfection through intratumoral application. Now a multitude of agents are being investigated for their antitumor activity by systemic application. Three major classes of agents are being explored: Antibodies to extracellular proteins such as antibodies to VEGF and EFG receptor, small molecules such as tyrosine kinase inhibitors and proteosome inhibitors, and antisense oligonucleotides such as antisense molecules against the antiapoptotic protein bcl-2. For some of the new targeted agents there are already phase III data available. Virtually all of these studies focused on the question, whether the addition of target agents to chemotherapy would be superior to chemotherapy alone. Unfortunately in lung cancer, these trials have been negative so far, including the studies on matrix metalloprotein inhibitors, the studies with the antisense oligoncleotide against protein kinase Cα, the studies with the EFGR thyrosine receptor antagonist gefitinib. Phase III results on the VEGF antibody bevacizumab in lung adenocarcinoma and the bcl-2 antisense oblimersene are pending. Major knowledge has been gained from the clinical development from gefitinib, a drug that has been approved for third line treatment of non-small cell lung cancer in several countries, an new questions have arisen: Which of the new target therapies should be given concomitant and which sequential with chemotherapy, on what bases could patients responding to targeted treatment be preselected, and how could one predict which tumor depends on which molecular pathway? To answer these questions it has become necessary to integrate molecular analysis of tumors on all patients giving consent to participate in clinical trials.

737

Integration of functional imaging (PET) into radiotherapy planning of non-small cell lung cancer

K. De Jaeger[1], E.F.I. Comans[2]. [1] *The Netherlands Cancer Institute, Radiotherapy Department, Amsterdam, The Netherlands;* [2] *Free University Hospital, Clinical PET Center, Amsterdam, The Netherlands*

Positron Emission Tomography (PET) using 18-fluoro-2-deoxyglucose (FDG) is a functional imaging technique that relies on the fact that most neoplasms have an increased glucose metabolism as compared to normal tissue. The PET tracer, ^{18} FDG, is a positron emitter and can be measured using (preferentially) a dedicated (full ring) PET scanner. FDG-PET provides metabolic activity of tumor cells but lacks precise anatomic information. It is now well-established that PET is significantly more accurate than CT to detect locoregional lymph node spread and distant metastasis in NSCLC. The addition of PET to conventional staging procedures contributes to a better staging and selection of NSCLC patients that can benefit from radical/curative RT.

The conventional imaging modality for RT planning is CT. CT provides electron density information, which is required for dosimetry calculations. As PET provides a better staging of the mediastinum, the integration of PET data could assist the radiation oncologist to define the nodal target volume more accurately, especially in RT dose escalation protocols and concurrent chemoradiation schedules in which the elective nodal irradiation is often omitted. In addition, for patients with atelectasis, the information provided by PET can lead to significant reductions in irradiated lung volume. The development of techniques for image correlation has facilitated the integration of metabolic information provided by PET and morphologic information provided by CT. Moreover, very recently scanners became available that can combine acquisition of both PET and CT.

At present, the resolution of clinical PET scanners is limited. In practice, it is in the order of 7 mm. The gantry aperture is limited to 60 cm. This implies that the RT treatment position of the patient cannot always be reproduced on the PET scanner. Registration errors in the order of 4 mm can occur. Given the different FDG uptake intensity in each patient, an individual threshold value needs to be determined. Furthermore, no studies are available that have investigated the correlation between the true tumor extension on surgical specimens and both activity detected on PET and morphological changes visualized on CT. For such a study, correction for respiration artifacts during acquisition of PET and CT images would be mandatory. Several groups are studying the feasibility of a respiration gating technique to reduce motion artifacts in PET imaging of lung cancer.

PET is a promising complementary imaging technique to CT in the RT planning of NSCLC. It improves our ability to more accurately define the nodal target volume. It still needs to be evaluated whether the improvement of target definition by integration of PET will lead to a better intrathoracic tumor control.

738

Has the page turned for adjuvant treatments?

P. Van Houtte. *Institut J. Bordet, Department of Radiotherapy, Brussels, Belgium*

If surgery remains the keystone in the treatment of lung cancer, only one third of the patients will be alive 5 years later. Failures are related to local relapse, distant metastasis or second primary. Two meta-analysis have drawn the scene for adjuvant treatments. They demonstrated a clear detrimental effect of postoperative radiotherapy and alkylating agents while cisplatine based regimens yield a low non-significant benefit (less than 5%). Current trials are conducted aiming to demonstrate such low but important benefit. A problem with adjuvant chemotherapy is the low compliance of patients as observed in the recent ALPI trial. The negative impact seen in the PORT meta-analysis may be due to a poor radiation technique but then to disappear for stage III or N2 disease. This suggests perhaps a therapeutic effect due to a better local control as observed in some trials. Nevertheless, there is no place for radiation after a complete resection of a stage I or II tumour. So, an induction program with or without radiotherapy was believed to let to a better tolerance and efficacy. Five phase III trials have addressed the issue of induction chemotherapy with controversial results: the Rosell and Roth trials were positive for stage IIIa disease but included only 60 patients while Tsuchiya and Depierre trials were negative. The later trial was the only one to include a large number of patients (350 patients) and showed a positive effect in a subgroup analysis, stage I and II. Preoperative radiotherapy was tested in the 70's without success. Combined chemoradiotherapy was used in a large series of phase II trials including stage IIIa and b disease allowing the following conclusions: acute toxicity and surgical morbidity were increased while there was a higher number of complete pathological response (10-20%). So, before considering an induction program as a classical approach for non-small cell lung cancer, there is a clear need for more large scale and well designed phase III trials. Furthermore, better tools are necessary to identify the patients eventually candidate for an induction program: the current staging system is not always helpful as a T4 may be operated or not and there is not always a clear correlation between stage and tumour volume. Nevertheless, we should remember that any small benefit in such a common disease will have a great impact.

739

The role of chemotherapy

H.H. Hansen. *The Finsen Center Rigshospitalet, Dept. of Oncology, 5072, Copenhagen, Denmark*

Until recently the management of lung cancer has often been characterised by a negative therapeutic attitude among many physicians and wide variations occur from region to region influenced by variations and traditions, knowledge, health care systems, and available resources.

In the past decade we have, however, seen major changes in lung cancer treatment. First and foremost there is a more optimistic therapeutic approach using a combination of the major treatment modalities: surgery, chemotherapy and radiotherapy applied concurrently and/or sequentially in early stage disease.

Small cell lung cancer (SCLC) is characterised by a higher metastatic potential with early spread to organs outside the lung. SCLC is also more a sensitive tumour than non-small cell lung cancer (NSCLC). Chemotherapy is therefore the cornerstone of treatment, and it is combined with radiotherapy to the chest in patients staged as having localised disease. Frequently used combinations are etoposide and platinum analogues given for 4-6 months. Major issues when applying chemotherapy in SCLC are: dose intensity, maintenance therapy, treatment at relapse, choice of drugs in the elderly patients, or patients with poor performance status.

For NSCLC chemotherapy is applied either alone or combined with radiotherapy and/or surgery in stage III and IV, while the role as adjuvant therapy in stage I and II is uncertain at present. As second line treatment single agent chemotherapy results in both prolongation of life and quality

of life improvement. New therapies with molecular targets have been developed and gaining ground in the treatment of NSCLC.

References

[1] Heine H Hansen. An update on management of lung cancer. Acta Oncologica, Vol. 41, No. 6, pp. 500-506, 2002.
[2] Kell Østerlind Chemotherapy in small cell lung cancer. Europ. Respir. J. Vol 18, pp. 1026-43. 2001.
[3] The role of new agents in the treatment of non-small cell lung cancer. Linda E Bröker, Guiseppe Giaccone. European Journal of Cancer 38m pp, 2347-2361, 2002.
[4] Lung Cancer Therapy annual III. Heine H Hansen, Paul A Bunn Jr. Martin Dunitz, London. In press 2003.

740

Secondary cancer as a side-effect to treatment of malignancies

J.D. Boice. *International Epidemiology Institute, Suite 550, Rockville, USA*

The success of cancer treatments carries with it the possibility of developing a new cancer later in life. Data compiled by the NCI Surveillance, Epidemiology and End Results Program indicate that second cancers, taken together, now appear as the fourth or fifth most common tumors. While lifestyle, other environmental, and genetic factors contribute to the second cancer burden, so do the therapies used to prolong life. Thus, it is of clinical and public health importance to evaluate carefully the occurrence of second cancers as they relate to curative treatments, and where possible, to develop preventive strategies. The study of cancer following radiotherapy (RT) provides data on both high dose (e.g., direct exposure to organs in the radiation field) and low dose (e.g., scatter radiation to organs outside the primary beam) effects; interactions with other therapies (e.g., platinum and other chemotherapy may enhance leukemia development), genetic conditions (e.g., the tumor suppressor gene, retinoblastoma, influences RT-induced sarcoma), or environmental factors (e.g., smoking may potentiate RT-related lung cancer); as well as temporal and age patterns of radiation-induced cancer. The study of cancer following chemotherapy has primarily focused on secondary leukemia but data are emerging that other sites may occur in excess, including the bone and lung. The knowledge gained from patient studies has influence the choice of therapies with cranial and spinal irradiation for childhood leukemia becoming less common, as has adjuvant radiotherapy for breast cancer; and alkylating agents with less leukemogenic potential have replaced more leukemogenic combinations such as MOPP. Important large studies will be summarized, including patients treated for Hodgkin's disease, cervical cancer, and breast cancer and children treated for retinoblastoma, leukemia and other cancers.

741

Late effects of paediatric bone marrow transplantation. Results of a single institution.

O. Oberlin[1], C. Soler[1], P. Nottoghem[1], D. Valteau[2], E. Benahmou[1], N. Corradini[1], M.C. Mathieu[1], O. Hartmann[1]. [1] *Institut Gustave Roussy, Pediatrics, Villejuif, France;* [2] *Institut Gustave Roussy, Statistics, Villejuif, France*

Many children are surviving bone marrow transplantation (BMT) and require long-term follow-up care. The number of late BMT survivors is expected to increase as new indications for transplant emerge and as supportive care improves. Long-term survivors bear special risks and need particular types of screening, prevention, and treatments. Risks for long-term survivors relate to the high-dose chemotherapy used as conditioning for BMT but also to conventional chemotherapy received before BMT. The quality of survival and the total burden of late morbidity were evaluated in 91/120 patients with minimum survival of 5 years (median 9; 5-19) after BMT for solid tumor in our Institution since 1980. Conditioning regimens were various, according to diagnosis and periods, but contained busulfan 56% (median dose 600 mg/m2) of the patients (pts) %. None of the patients received radiation therapy (RT) as part of the regimen but 45 pts (50%) had received previous radiation.

Median age at evaluation was 9 years. Growth and endocrine function, cardiovascular, pulmonary, hepatic and renal status, other organ toxicities, neuropsychological outcome and second malignant neoplasms (SMN) were recorded.

GH deficiency was observed in 9 pts, of whom 5 did not have cranial irradiation. The difference between the weight and the height-SD value at BMT and at evaluation was +0.11SD and –0.6DS respectively. 64% of the female population have an ovarian damage: 100% after busulfan and 29% after busulfan free regimens. Only 1/16 of the non irradiated boys have normal testicular function after busulfan, whereas 20% of the males treated with other regimens.

Eleven pts had lung abnormalities, symptomatic in 8 (4 had previous mediastinal RT, 2 had restrictive sd before BMT and 1 a neurological pathology). Nine pts had cardiotoxicity with SF<30%, symptomatic in 2 (of whom one underwent cardiac transplantation). All of them had been treated by anthracyclines before BMT.

One pt had grade 2 and 6 had grade 1 glomerular toxicity. 26% of the evaluated pts had a minor tubular function failure. Among pts treated with a busulfan containing regimen, 17% developed a focal nodular hyperplasia of the liver without any clinical or biological dysfunction.

All of pts with severe ototoxicity (grade 3 and 4) had previously received platinum-coumpounds treatment.

The majority of the pts tested had normal IQ (above 85). The incidence of IQ scores below 75 was 17% for the FSIQ, 17% for the VIQ and only 6% for the PIQ. The educational and professional outcomes of most pts were within the normal range.

Four pts developed an SMN (1 AML, 1 sarcoma, 1 melanoma, 1 basocellular carcinoma)

In conclusions: Gonadal dysfunction was common in pubertal survivors of both genders. The observed cardiotoxicity is likely realted to anthracyclines given before BMT. These results suggest also that the cognitive and social function of children is not detrimentally affected 5 years post BMT.

742

Long-term risk of cardiovascular disease following treatment for cancer

F.E. van Leeuwen[1], M.J. Hooning[1], B.M.P. Aleman[2]. [1] *The Netherlands Cancer Institute, Department of Epidemiology, Amsterdam, The Netherlands;* [2] *The Netherlands Cancer Institute, Department of Radiotherapy, Amsterdam, The Netherlands*

Radiation-induced heart disease includes a wide spectrum of cardiac pathologies, such as pericardial disease, myocardial dysfunction, valvular heart disease, electrical conduction abnormalities and coronary artery disease. In recent years, there has been increasing evidence that, with long-term follow-up, radiation-induced coronary artery disease will probably pose the most serious health hazard of irradiation (RT) of the heart. Chemotherapy (CT) with anthracyclines has long been known to induce cardiomyopathy, with a cumulative dose-response effect. The risk of treatment-induced heart disease has been studied most extensively in survivors of Hodgkin's disease (HD), breast cancer and childhood cancer.

Mortality from CVD has been extensively examined in several large series of *HD* patients. In the largest study (n=4665; treatment period: 1940-1985), the risk of death from myocardial infarction (MI) following mediastinal irradiation was 2.6 fold increased as compared with the general population. The relative risk (RR) was substantially lower for patients irradiated after 1967. The cardiac mortality risk in a cohort of 2232 HD patients treated at Stanford University between 1960 and 1991 was 3.1 times increased as compared to the general population. RRs of acute MI death and death from all other cardiac diseases were 3.2 and 2.9, respectively. The routine blocking of the left ventricular and subcarinal regions introduced in 1972 did not affect the risk of acute MI death, but significantly lowered the RR of death from all other heart diseases (5.3 before 1972 vs 1.4 thereafter). At 20 or more years after HD treatment, the RRs of acute MI death and death from all other cardiac diseases were 5.6 and 8.8, respectively. Age at irradiation turned out to be a major determinant of mortality from heart disease, with by far the highest RR observed for patients irradiated before age 20, and little excess risk associated with RT after age 50. Recently, we also demonstrated a 6-fold increased RR of death from cardiac diseases in 1261 HD patients treated in the Netherlands between 1965 and 1987 (median follow-up time, 17.8 years) before the age of 40. The RRs for dying of CVD were increased especially for patients treated at the age of 20 years or less (RR=13.6). When these patients attained older ages, we observed trends of decrease for the elevated mortality from CVD. For all patients the increased RRs of death from CVD seemed to level off after 20 years, albeit based on small numbers.

Mortality from CVD in patients irradiated for *breast cancer* has been extensively studied, with inconsistent results. Since excess risk has been rather consistently observed for survivors treated before 1970, the controversy concerns in particular breast cancer patients irradiated with modern techniques. In the Netherlands we recently examined CVD mortality in a series of 3900 breast cancer survivors treated between 1970-1981 (median follow-up, 12.6 years). Compared to the general female population, the number of cardiovascular deaths in the study population was within the