Teaching Lectures

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NSCLC second line treatment - worth the effort?

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The modest impact of chemotherapy on survival duration in patients with NSCLC has led most medical oncologists to ignore the effect of 2nd line treatments. Nevertheless, more and more active therapeutic strategies in initially inoperable NSCLC must make consider salvage therapies including surgery, radiotherapy or chemotherapy in the survival analysis of patients enrolled in prospective trials as these additional therapeutic modalities may provide a substantial benefit on survival. Most agents used in advanced NSCLC have been evaluated in small phase II studies. Response rates were generally <10% with a clear lack of impact on survival and, until recently, there was no standard accepted treatment of patients who had already received platin-based chemotherapy. In spite of these figures a great proportion of patients ask for 2nd line treatments. Given that palliation is the main goal of chemotherapy for advanced NSCLC patients, it is essential that prospective trials are also designed to address this issue. Docetaxel has been one of the first cytotoxic drugs showing a clear activity in 2nd line in patients with advanced NSCLC in phase II studies at doses of 60 to 100 mg/m2 given every three weeks and two randomized studies were designed to evaluate its impact on survival of such patients. The first study, TAX 317, compared docetaxel with best supportive care. Fifty five patients received docetaxel at 75 mg/m2, 48 received docetaxel at 100 mg/m2 and 100 were in the control group. A statistically significant improvement of survival was observed with docetaxel 75mg/m2 versus BSC ($p<0.01$). Quality of life parameters also favored docetaxel-treated patients. In the second phase III trial, TAX 320, docetaxel at 75 mg/m2 was compared to docetaxel at 100mg/m2 and to vinorelbine or ifosfamide according to the first line regimen. A total of 373 patients were included; partial responses were 7%, 11% and 1% respectively ($p=0.001$). The survival rate at 1 year was higher among patients treated with docetaxel 75mg/m2 than among those receiving vinorelbine or ifosfamide ($p=0.025$). Again in this study, there was a quality of life improvement favoring docetaxel in several items. Other cytotoxic agents still in development have shown promising results in 2nd line therapy and might play a role in the future. Another category of agents, targeted drugs, have also been reported as active in patients with pretreated NSCLC during the phase I studies. The tyrosine-kinase inhibitor IRESSA (ZD 1839) has shown some provocative responses during the phase I study at doses ranging from 150-700 mg/m2/day orally. A Phase III study is ongoing after standard induction chemotherapy in patients with advanced NSCLC. OSI-774, another EGF receptor tyrosine-kinase inhibitor, has also shown promising effects in phase I. This generation of new agents together with classical cytotoxic drugs might favorably alter the outcome of patients with advanced NSCLC in the next future and medical oncologists will have to take into account the impact of these treatments before judging first line treatments with overall survival as the main objective.

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Follicular Non-Hodgkin's Lymphoma (NHL)

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56,200 new cases of NHL are expected to be diagnosed in in the United States in 2001. For reasons that are not fully understood, the number of new cases per year has nearly doubled in the past three decades. Follicular lymphoma comprises 70% of the indolent lymphomas reported in American and European clinical trials. Most patients with follicular lymphoma are over age 50 and present with widespread disease at diagnosis. Nodal involvement is most common, often accompanied by splenic and bone marrow disease. Despite the advanced stage, the median survival ranges from 8 to 12 years. However, the vast majority of patients with advanced stage follicular lymphoma are not cured with current therapeutic options. The rate of relapse is fairly consistent over time, even in patients who have achieved complete responses to treatment.

The approval of rituximab (Mabthera), an unconjugated chimeric antibody against the CD20 antigen for the treatment of relapsed follicular B-cell NHL marked a milestone in the development of antibody-treatments. Newer aproaches like radioimmunoconjugates with myeloablative activity induced response rates of 80-100% in heavily pretreated patients.

Various clinical trial combining these new agents with conventional therapies are currently ongoing to determine weather these new biologic agents will alter the natural history of this disease in NHL patients.

Long-term follow-up on high-dose therapy (HDCT) suggests a potential role for this modality. Prolonged Fredom from relapse can be achieved in patients with follicular lymphoma after HDCT, but as yet there is no survival advantage compared with conventional treatment.

In conclusion, therapeutic options in follicular NHL include watchful waiting, purine nucleoside analogs, oral alkylating agents and combination chemotherapy. Interferon, monoclonal antibodies, radiolabeled monoclonal antibodies, vaccines, and autologous or allogeneic bone marrow or peripheral stem cell transplantation are under clinical evaluation.

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Radiotherapy directed gene therapy

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Radiotherapy is the major modality for the treatment of many cancers. Radiation-directed gene therapy exploits the fact that radiation is directed to the tumour volume, the temporal and spatial control of gene expression is therefore achievable by radiation for any genes delivered to the tumour. In the experimental models developed so far, the therapeutic genes are controlled by locating them downstream of the promoter regions of genes that show up-regulated expression following exposure to ionising radiation. For example, the 5' regulatory region of the early growth response (EGR-1) gene has been used to drive expression of the cytotoxin tumour necrosis factor-a (TNF-a). We have adapted this strategy by combining novel synthetic radiation-responsive gene promoters with gene-directed enzyme/prodrug therapy (GDEPT). This approach should be applicable to all cancers treated by radiotherapy. However, to ensure that gene expression could be achieved by radiation doses used clinically (2 Gy and below) we have designed and constructed a series of synthetic radiation-responsive promoters based on elements from the EGR1 promoter. We have extended the use of synthetic radiation-responsive gene promoters in combination with the Cre/LoxP recombinase system of bacteriophage P1. Using this system, a single dose of radiation can lead to HSV-tk gene expression via the strong constitutive cytomegalovirus (CMV) promoter, thereby producing a substantial amplification of the activation signal. This also ensures efficient and sustained expression of the therapeutic gene in the tumour volume after the radiation stimulus has been withdrawn. Since this system requires two gene promoters to function, the potential exists for combining a radiation-responsive promoter to activate the system with another selective promoter to control expression of the therapeutic gene. Ultimately, the success of gene therapy will dependent on the efficient delivery of transgenes to the tumour site. However, the development of strategies or vectors that can offer, or achieve, tumour targeting after administration will play a significant role in the success of cancer gene therapy. This teaching lecture aims to review the field of radiation-directed gene therapy and also other gene therapy targeting approaches.

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Molecular Biology and the Surgeon

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One hundred and fifty years ago Joseph Lister applied the new science of microbiology to solving the problem of sepsis in the surgical patient. The

surgical oncologist should be equally aware of today's new science of molecular biology and the opportunities it presents in the diagnosis and managment of the cancer patient.

Understanding the molecular aetiology of cancer offers an opportunity of earlier intervention by applying screening to high risk groups, for example, in subjects of genetic risk of breast or colon cancer or using molecular markers to screen for cells exfoliated from cancer, as in bladder or colon cancer. It also enables different interventions such as cyclo-oxygenase inhibitors to prevent the progress of colonic polyps.

In established cancer the genetic alterations can be utilised to not only predict outcome but also to predict outcome for theory and ultimately to devise new therapies. In breast cancer the over-expression of hormone receptors have long been established as a target for therapy but this is now extended to the use of anti-HER2 treatments.

This talk will discuss the potential utility for the surgical oncologist.

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The Kaposi's sarcoma associated human herpesvirus 8 - epidemiology and pathogenicity

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The epidemiology of Kaposi's sarcoma (KS) amongst North American and Northern European patients with AIDS suggests that an infectious agent other than HIV is involved in its pathogenesis. Epidemiological data indicate that human herpesvirus 8 (HHV-8), also termed Kaposi's sarcoma associated herpesvirus, is the sought-after agent. DNA of HHV-8 is invariably found in all forms of KS where the virus is present in the KS spindle cell. In contrast, HHV-8 DNA is not regularly detected in most other malignancies. Although current serology does not allow to assess the HHV-8 prevalence in the general population with certainty, high titers of HHV-8 antibodies are almost exclusively found in KS risk groups. In addition, HHV-8 seroconversion has been shown to precede KS development. The mechanisms and genes involved in HHV-8 pathogenesis are less clear. HHV-8 belongs to a family of transforming viruses, and several candidate oncogenes have been identified by using rodent fibroblast transformation assays. In addition, the virus encodes and induces several cytokines and angiogenic factors. This is of particular interest as models of KS pathogenesis developed before the discovery of HHV-8 emphasized the importance of inflammatory cytokines. However, expression of most of these genes could not be shown in latently infected tumor cells. Only the virus encoded cyclin D homolog, a nuclear antigen encoded by open reading frame 73, and the viral FLICE inhibitory protein have been shown consistently to be transcribed in the majority of latently infected cells. In addition, a novel HHV-8 encoded transcription factor with homology to the family of interferon response factors is expressed in latently infected B-cells. Although the expression pattern of viral genes in KS is not certain yet, it appears likely that the pathogenetic role of HHV-8 in KS may be rather complex and differs from other virus-induced malignancies.

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Thyroid cancer after irradiation

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External irradiation to the neck during childhood increases the risk of papillary thyroid carcinoma (PTC). The latency period is at least 5 years. The risk is maximal at 20 years. The risk is increased after a dose to the thyroid as low as 10 cGy. Above this dose there is a linear relationship between the dose (up to 1500 cGy) and the risk of carcinoma. Risk factors include a young age at irradiation and above age 15 years the risk is not increased; female sex and familial susceptibility. In children exposed to 1 Gy to the thyroid, the excess risk is 7.7.

A tumorigenic effect on the thyroid of iodine isotopes in children has been suggested by the increased incidence of PTC in the Marshall Islands after atomic bomb testing, and more recently in Belarus and Ukraine, as a consequence of the Chernobyl accident. However, there is no evidence that the risk of PTC is increased in adults given 131 I; the increased incidence of thyroid carcinomas observed in western countries since 25 years is not related to the Chernobyl fall-out, but rather to more extensive thyroid examination in the general population.

RET/PTC rearrangements are found in 60–80% of radiation induced PTC and in only 5–15% of PTC occurring in the absence of radiation exposure.

Subjects exposed to radiation during childhood should be submitted to follow-up. Any thyroid nodule warrants a complete work-up including a fine needle aspiration biopsy. The initial treatment, follow-up and long term prognosis are similar to those of PTC patients with no history of neck irradiation.

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The colorizing of cancer cytogenetics

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Karyotype analysis has depended on chromosome banding techniques since their introduction around 1970. The information thus obtained is relevant for diagnosis, prognosis, and disease monitoring in patients with hematologic malignancies and increasingly also in solid tumors. Some technical developments in recent years have helped bridge the gap between chromosome-level and molecular-level investigations. Interphase or metaphase fluorescence in situ hybridization (FISH) with chromosome- or locus-specific DNA probes can identify rearrangements too subtle or too complex to be disclosed by chromosome banding alone. On the negative side, this type of investigation only reveals those aberrations one tests for and is therefore not suitable for the initial screening of tumors. Comparative genomic hybridization (CGH), on the other hand, which uses tumor genomic DNA and normal DNA as competing probes and normal metaphases as templates, is a genuine screening method that detects copy-number changes. CGH does not detect balanced rearrangements, however, nor does it detect differences among cells. Spectral karyotyping (SKY) and Multiplex-fluorescence in situ hybridization (M-FISH) use a pool of painting probes that label each chromosome with a different fluorochrome combination, and are particularly promising to characterize complex interchromosomal rearrangements. It does not detect intrachromosomal changes, however, and breakpoint assignment is unreliable. The last addition to the field is Cross-species color banding (RxFISH), which uses probes originating from flow-sorted, differentially labeled gibbon chromosomes. Because of the extensive sequence homology between gibbon and human DNA (98%) and the many chromosomal rearrangements that have occurred during evolution, the hybridization of these probes onto human metaphases results in a specific color banding pattern for each human chromosome. The combination of these new FISH technologies with standard chromosome analysis will ensure that the future of cancer cytogenetics is bright and colorful.

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Cure of chronic myeloid leukeaemia

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Chronic myeloid leukaemia (CML) is thought to be due acquisition of a BCR-ABL fusion gene in conjunction with Ph chromosome in a single multipotential haemopoietic stem cell whose progeny gain a proliferative advantage and eventually replace all normal haemopoietic tissue. Conventional cytotoxic drugs alone or in combination are effective in reducing the size of the leukaemia cell mass but do not adequately differentiate between leukaemic and normal cells; moreover some Ph-positive stem cells may be 'deeply' quiescent and thereby escape the action of anti-leukaemic drugs. Experience with allogeneic stem cell transplantation (allo-SCT) over the last 20 years suggests that the majority of those who survive 5 years are probably cured because (a) the incidence of relapse thereafter is very low, and (b) most remain persistently negative for BCR-ABL transcripts when studied by the most sensitive RT-PCR. The mechanism of cure is uncertain but much evidence suggests that it is due to a combination of the drugs and radiotherapy used as conditioning and a graft-versus-leukaemia (GVL) effect mediated by donor lymphocytes. The possibility that cure can be mediated by a GVL effect alone or in association with reduced-intensity conditioning is now being tested in many specialist units but conclusive results are not yet available. The biological basis of GVL remains unknown but candidate target antigens include: BCR-ABL oligopeptides, proteinase-3, WT1, minor histocompatibility antigens. A variety of immunisation strategies are now being designed for patients not eligible for allo-SCT and some have entered the clinic. Meanwhile the ABL kinase inhibitor STI571 has proved remarkably effective at reducing the leucocyte count and restoring Ph-negative haemopoiesis in previously untreated patients; currently it seems unlikely that this agent alone will cure more than a small proportion of patients but combinations of STI with IFN, cytarabine or other agents may do so; moreover the possibility of using STI in conjunction with an autograft procedure is attractive. The issue of whether a GVL effect is a necessary prerequisite for cure of CML may be answered within the next ten years.