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