Teaching Lectures

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The role of neoadjuvant and adjuvant chemotherapy in non-small cell lung cancer

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Combined modality therapy is the cornerstone for better results in the treatment of certain subsets of non-small cell lung cancer (NSCLC). Among various therapeutic strategies adjuvant and neoadjuvant chemotherapy (CT) represent the most promising ones, though today neither of the two can be considered a standard treatment. Adjuvant CT represents the effort to improve long term results with systemic therapy in operable patients in whom the risk of relapse is considered high on the basis of surgical staging ($T > 1$ and N_1 or N_2). While past experiences were negative, the recent metanalysis gave support to the validity of the concept of adjuvant CT showing a small but definite advantage for the patients who were treated with a cisplatin containing regimen. Some important clinical trials are under way, also on an international basis, and their status will be reported.

Nonadjuvant CT is a more complicated issue because of the methodologic difficulties and different criteria for selection of patients for clinical trials. The phase II studies so far conducted have demonstrated that neoadjuvant CT is feasible, surgery can be performed in responding patients, and toxicity is tolerable.

What is still unclear is if neoadjuvant CT improves survival, if radiotherapy is important and if so in what sequence with CT and which CT should be used. The answers to these questions will only come from the randomized large trials that are under way, each of them addressing a specific problem.

1020

Apoptosis in cancer

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The development of cancer cells may be a consequence of increased cell survival and decreased cell death (apoptosis). Apoptosis may be induced by withdrawal of growth factors and survival factors or alternatively may be induced by signalling through cell surface molecules such as CD95 (APO-1/Fas). CD95 is expressed on many cell types including activated T and B cells. Following multimerization of CD95 by its natural ligand or agonistic antibodies, a death inducing signalling complex is formed that initiates proteolytic cleavage of ICE/Ced-3 proteases, crucial for transmission of the apoptotic signal. The CD95 ligand is produced by activated T cells and constitutively expressed in a variety of tissues. In activated T cells, T cell receptor mediated apoptosis involves an autocrine suicide via CD95 receptor/ligand interaction. Disturbances of the CD95 system are involved in a variety of pathological conditions and human diseases. Thus, mutations of the receptor have been found in patients with a syndrome of lymphoproliferation and autoimmunity. Recently we discovered that cytotoxic drugs previously thought to inhibit cellular proliferation mainly by metabolic function or DNA damage, uniformly activate the CD95 system in chemosensitive cells. Upon incubation with cytotoxic drugs such as doxorubicin, CD95 ligand is produced and initiates a death cascade in an autocrine or paracrine manner. Inhibition of CD95 induced apoptosis in chemosensitive tumor cells leads to drug resistance. Conversely, drug resistant cells are resistant to CD95 induced apoptosis. Inhibition of ICE/Ced-3 proteases involved in the CD95 pathway also confers drug resistance to tumor cells. The discovery of cross resistance between CD95 induced apoptosis and cytotoxicity of anticancer drugs opens new perspectives for treatment of tumors and to overcome drug resistance.

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Metastases of unknown primary tumor (UPT)

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Metastases of UPTs, mainly diagnosed in liver, lung, bone, and lymph nodes, account for 4% of all malignancies; 24% of pts with UPTs have multiple metastases. UPTs are slightly more often diagnosed in male than in female, the majority of patients are in the 6th decade of their live. When UPT is diagnosed a thorough physical/clinical examination and diagnostic evaluation with serum tumor markers, CT, MRI, PET, laparoscopy or pan-endoscopy is performed to find the primary tumor. Based on the ultimately established pathological diagnosis, adenocarcinoma (50–60%), squamous carcinoma (5–8%), poorly differentiated carcinoma/adenocarcinoma (30–40%), a tailored treatment plane is outlined based on patient condition and the site of the UPT. The goal of palliative treatment, which can consist out of palliative surgery and/or radiation treatment, and/or systemic hormonal treatment, is to improve (local) tumor control and/or prevent associated morbidity, and therefore improving quality of life. There is seldom an indication for palliative chemotherapy. Although the prognosis of UPTs is very poor, with exception of the unknown squamous cell UPT's in the head and neck area, adequate palliative treatment has a substantial psychological benefit for the patient.

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What have we learnt during 60 years of surgery for pancreatic cancer?

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Even though Allessandro Codivilla in Bologna performed the first pancreaticoduodenectomy in 1898 and Walter Kausch was the first with a surviving patient in 1909 it was not until Allen Oldfeather Whipple (New York) in the second half of the 1940's published his series of operations that this kind of surgery was given attention. Since then there have been several steps in its evolution:

1950's – trying the technique in a larger series
1960's – identifying the limitations of indications
1970's – minimizing the mortality, extending the operations
1980's – minimizing the morbidity, increasing survival
1990's – identifying the factors important for quality of life

Today the challenge must be to keep the mortality as near to zero as possible and refine the techniques to further decrease the complication rate. Radical surgery will most probably need adjunct therapies for eradication of local recurrencies (IORT?) and liver metastases (bio-chemotherapy?) to increase survival, but this must be balanced against the total quality of life for the patients. During the next decade the surgeons together with nurses, gastroenterologist, endoscopist and interventinal radiologist must be able to palliate the patients better in less extensive ways and do it more cheap.

We have learnt a lot during 60 years, but we are not even halfway yet...

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No abstract

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Thyroid cancer – Standards and own views

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Thyroid cancer is a rare tumor with a high diagnostic challenge to be detected among the high frequency of thyroid lesions. Various different histologic entities such as differentiated thyroid carcinomas (DTC: papillary, follicular), medullary thyroid cancer (MTC), anaplastic thyroid cancer (ATC)

and nonepithelial tumors (lymphoma, sarcoma etc.) have to be considered. Standard therapy for DTC is total thyroidectomy including central lymph node dissection. Additional unilateral neck dissection should be considered in T2 to T4 tumors and is mandatory in suspected or proven regional lymphatic spread. Limited radicality meaning lobectomy or even subtotal resection in occult tumors is adequate for small encapsulated papillary (<1 cm; T1) and microinvasive follicular (<1 cm; T1) tumors with no necessity of additional radioiodine therapy. MTC might be sporadic (SMTC, unifocal) or familial (FMTC, multifocal) requiring thyroidectomy always and neck dissection unilaterally in SMTC and bilaterally in FMTC. Genetic screening allows early detection of the disease and thus thyroidectomy only seems to provide appropriate radicality. In ATC radiochemotherapy is the treatment of choice and operation is rarely indicated and only suitable for decompression or debulking.

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Introduction to tumour immunology and cancer vaccines

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Since the turn of the century there have been many attempts to try to induce remissions in tumours by stimulating the immune system. Perhaps the grandfather of clinical application was William Coley, a New York Surgeon who noticed that patients with severe septicemia sometimes underwent remission of their tumours. Whilst trying to identify the active component of the infection, he came up with a bacterial cell wall mixture which subsequently became known as 'Coley's Toxins'. Other investigators tried a variety of autologous and allogeneic cell based vaccines with limited success.

More recently the use of cell based vaccines has been re-visited under the guise of gene therapy. Autologous tumours are difficult to grow and stabilize on an individual basis and allogeneic vaccines have been considered by a number of investigators. The use of cells allows one to present a variety of tumour antigens to the immune system. Boon and his colleagues have identified several tumour antigens recognised by cytotoxic T-cell lymphocytes from patients at the peptide level and a number of new antigens have been defined and their epitopes and HLA associations documented. This has lead to a number of studies using peptides such as MAGE, MART and tyrosinase with a variety of antigen presenting techniques such as culture dendritic cells.

What is urgently needed is parameters to know which patients to treat, what immune parameters are required in order to ensure a response and perhaps most importantly when to stop treatment with a specific protocol. The technology to address these questions is now available and it only remains to apply the most appropriate ones to the correct clinical questions.

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Current developments in the treatment of chronic myeloid leukemia

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Currently, allogeneic bone marrow transplantation (BMT) is the only curative treatment available, but is only applicable in a minority of patients (± 20%) for whom a HLA identical related or unrelated donor can be found and who are under the age of 50–55 years. Results have improved over the last 10 years, largely due to a reduction of transplant related mortality. The relapse rate after BMT depends on the number of T-cells in the graft and recently it has become clear that an established relapse after BMT can be treated effectively by donor lymfocyte infusion (DLI) without the addition of chemotherapy.

Patients, lacking an allogeneic donor, are currently treated with Interferon-Alpha (IFN-α) and/or Hydroxyurea. IFN-α has been shown to prolong survival, but the beneficial effects of IFN-α seem to be restricted to a subgroup (15–20%) of patients, who achieve a major cytogenetic response.

Current treatment protocols are designed to improve the number of cytogenetic responders by combining IFN-α with chemotherapeutic agents, such as low-dose Cytarabine. Autologous stem cell transplantation followed by IFN-α may also improve survival and several approaches are underway to address the value of that treatment modality.