The described angiogenesis-independent tumor growth and the uncoupling of invasion and angiogenesis, represented by the cancer stem cells and the cells derived from them respectively, points at two completely independent mechanisms that drive tumor progression. The present work underlines the need for developing therapies that specifically target the cancer stem cell pools in tumors.

88 INVITED

Exploiting biological targets for therapy

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Current treatment of glioblastomas relies on surgical resection, radiotherapy and chemotherapy. However, the efficacy of these treatments is still limited and new therapeutic approaches based on the understanding of brain tumor biology are emerging. High expression of the EGF receptor by tumor cells, activation of the PI3K/Akt and the Ras/Raf pathways, secretion of protease by the tumors represent interesting targets for new selective drugs under development. Numerous antiangiogenesis agents are currently in preclinical development and early clinical trials, including VEGF and VEGFR antibodies and small molecule inhibitors.
So far, most of these new drugs have shown disappointing results in phase 2 trials. Combination of these drugs, or association with radiotherapy or chemotherapy might increase their efficacy. Translational research will probably identify sub-groups of patients with specific tumor molecular profiles, allowing tailored or specific therapies based on collections of genetic alterations. In addition, the recent development of convection-enhanced delivery technique allows the administration of drugs which do not cross the blood-brain-barrier, such as selective toxins, antisens or immunostimulating oligonucleotides. Some of these drugs are currently being tested in randomized phase 3 trials.

89 INVITED

Exploiting biological targets together with radiation

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Glioblastoma multiforme (GBM) and high grade astrocytomas are heterogeneous tumors and are characterized by areas of severe hypoxia by virtue of abnormal tumor vasculature giving rise to poor tumor blood perfusion and high interstitial fluid pressure. This represents significant challenges for cytotoxic therapy. It is well appreciated that hypoxia leads to radioresistance because of lack of oxygen to facilitate DNA damage by radiation-induced free radicals. In addition, hypoxic conditions create a microenvironment in which tumor cells become more angiogenesis dependent, more apoptosis resistant, more capable of existing under hypoxic conditions and more malignant because of the development of genomic instability and mutant genotypes impacting on apoptosis/survival signaling pathways. In GBM, the mutant genotype includes loss of the PTEN tumor suppressor, constitutive activation of the PI3K/Akt/mTOR signaling pathway and EGFR upregulation, amplification and/or mutation. These genetic changes can influence the response to ionizing radiation. Preclinical data will be presented on the use of signal transduction molecules including antiangiogenic therapies, combined with ionizing radiation. Issues including the spectrum of preclinical models, optimal timing of targeted agents and the integration with chemotherapy, will be discussed. Finally, novel phase I strategies to move laboratory findings rapidly into the clinic will be presented.

90 INVITED

Biological predictors for chemotherapy response

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Clinical parameters (age, performance status, tumor resectability, histology + tumor grade) are important prognostic factors. Understanding of tumor biology and identification of molecular markers are crucial for future trials. However, many markers may merely reflect a different natural history and do not contribute to individual patient management. Oligodendroglioma with LOH 1p/19q has been associated with high response rates and improved survival, although the underlying genetic defect has not been identified yet. In anaplastic oligoastrocytoma and oligodendroglioma 2 trials evaluated PCV-chemotherapy (before/after radiotherapy (RT)), compared to initial treatment with RT alone. Neither trial demonstrated improved survival with early chemotherapy administration; progression-free survival was prolonged in the chemotherapy groups. Even in the subset of patients with LOH 1p/19q, considered the most sensitive to chemotherapy, no improvement was seen. These patients had prolonged overall survival irrespective of treatment, thus characterizing a distinct pathologic entity. Improved outcome has also been suggested for patients with a methylated promoter of the DNA repair gene MGMT. Tumors with a methylated MGMT gene promoter, thus a silenced gene are unable to repair some of the DNA damage induced by the chemotherapy. In glioblastoma improved survival was demonstrated for temozolomide (TMZ) and RT. We showed that the benefit of the addition of TMZ chemotherapy was almost exclusively confined to patients whose tumors had a methylated (silenced) MGMT promoter. At 2 years, 46% of the pts treated with TMZ/RT and whose tumors were MGMT methylated survived, compared to only 14% for the pts with unmethylated tumors. Small molecule drugs targeting signaling pathways aberrantly activated in tumors will be central to future clinical trials. In glioblastoma the EGFR- and PI3K-pathway represent attractive targets. Promising are also strategies that aim at angiogenesis such as inhibitors of VEGF(R) or of integrins. It is likely that combination treatments are required. Since these strategies aim (mainly) at specific molecular targets it is mandatory to establish molecular profiles of the tumors for individualized treatment. Thus, common to all ongoing or planned trials is the absolute necessity of availability of tumor material for molecular profiling (paraffin-embedded or ideally fresh-frozen) in order to provide the patient the most adapted treatment.

Scientific Symposium
Pelvic relapses in gynaecology

91 INVITED

Overview of pelvic relapses in gynaecological cancer

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Presentation of pelvic relapses from gynecological malignancies depends on the origin of the primary tumor.
Ovarian cancer rarely relapses in the pelvis alone but the pelvic relapse may represent significant tumor burden. These recurrences are largely intraperitoneal. Nodal disease on the sidewalls as a sole site of recurrent tumor is rare in ovarian cancer. Management is going to depend on the treatment free interval since primary therapy. Surgery is an option with treatment free intervals greater or equal than one year, dependent on patient operability and the likelihood of being able to perform a complete tumor debulking. Radiation therapy is used in the exceptional case where relapse occurs in the pelvis only. Most patients will be managed by systemic chemotherapy.
In the tumors of vulva, endometrium and cervix, isolated pelvic relapse may occur with cervix cancer contributing to the majority of such patients. While radiotherapy is most frequently the initial treatment option chosen, it is important to distinguish two different forms of recurrence: A. Central occurrence, B. Sidewall occurrence.
Pelvic sidewall recurrence represents a challenging problem. Often characterized by invasion of adjacent muscle, vessels nerves and other organs, a variety of surgical options have been explored in these circumstances. While local control appears to be feasible more frequently with extensive surgery, extensive sidewall disease is also frequently characterized by occult hematogenous and/or lymphatic metastasis extending beyond the resectable area. New diagnostic techniques, for example, PET scanning may help to better select patients for this type of radical procedure. For most of the patients with recurrent tumor involving the pelvic sidewall, the available approach remains strictly palliative after the failure of radiation therapy. This would be the first treatment option as it still may offer a chance of cure in the not previously radiated patient. Chemotherapy and/or other medical interventions are strictly palliative in nature, while rare long term survivors have been reported with prolonged chemo- or hormonal therapy. Central recurrence, also after radiation therapy may be amenable to supra-levatorial or trans-levatorial exenteration giving the patient with this type of recurrence a 50% chance of cure if all tumor can be surgically resected. Expand the indications for radical surgery to encompass also some extension towards the sidewall. Also, the array of available reconstructive options has largely increased in recent years culminating in the concept “stoma-less exenteration”. This has greatly enhanced the acceptability of such procedures for the patient and contributed to a better quality of life.
In summary, pelvic relapse of gynecological tumors represents a challenging clinical situation that mandates individualized treatment options. Therefore, therapy should be performed at large referral centers.