Scientific Symposium (Sat, 24 Sep, 11:15−13:15)
Nanotechnologies for Targeted Drug Delivery

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Nanoplatforms for Targeted Drug Delivery

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The origin of the nano-delivery drug targeting approach for the treatment of cancer started in the 60's. This approach has led to a new generation of nanomedecines that are aimed at enhancing the efficacy of anti-cancer drugs and improving the patient's quality of life. The rational behind this new concept of nanotherapeutics relies on the use of nanocarriers that can help bioactive compounds to overcome critical biological barriers, i.e. degradation in the blood-stream, biodistribution and internalization by the target cells. Currently, important efforts are being oriented towards this goal and the prospect is that these nanotherapeutic strategies will soon represent a great milestone in cancer treatment.
During this presentation, a number of examples of nanocarriers designed in our laboratory for the targeted delivery of anticancer drugs will be overviewed. These nanocarriers, named nanocapsules, are composed of an oily container and a polymer corona. The container has the capacity to accommodate the anticancer drug and/or the adjuvant compound (i.e. immunomodulatory agent) and control their release. The polymer corona may have a multifunctional character, namely (i) to prolong the residence time of the drug in the blood stream, (ii) to target specific cancer cell populations, and (iii) to attach macromolecular adjuvants and drugs. This corona has so far been made of polymers such as polyglutamic acid, polyasparagine, polyarginine and hyaluronic acid. The results obtained until now for specific anticancer molecules, i.e. docetaxel and aplidin, have provided evidence of their enhanced uptake by cancer cells, modified pharmacokinetics and reduction of the systemic effects as a consequence of their association to the nanocapsules. Overall, during the presentation, the level of success achieved with these nanocarriers will be discussed.
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26 INVITED

Nanocarrier Pharmacokinetics and Pharmacodynamics: Watching Where Nanoparticles Go

Abstract not received

27 INVITED

Temperature Sensitive Drug Nanocarriers for Local Delivery

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Drug-loaded temperature sensitive nanocarriers such as liposomes were more than 30 years ago suggested for a new approach in local cancer therapy. At body temperature, a small molecular weight drug is stably loaded into the aqueous lumen of the liposome, which prevents rapid and unwanted distribution of the drug across all tissues. Upon heating to mild hyperthermia (T = 41−42ºC), which coincides with the melting temperature of the liposomal membrane, the lipid bilayer becomes leaky leading to a rapid and fast drug release. For local drug delivery application, the challenge is to maintain in a well defined target tissue hyperthermia in a non-invasive way for 30 minutes and more. Secondly, a non-invasive way to monitor the drug delivery process and achieved drug concentration is highly warranted.
High Intensity Focused ultrasound allows non-invasive heating to establish hyperthermia (40−43ºC) in almost any tissue that can be acoustically reached. MRI plays in this procedure a pivotal role thanks to its superb resolution for soft tissue as well as the possibility to acquire 3D temperature information. Consequently, MRI scanners emerged with an (high focused) focused ultrasound transducer embedded in the patient bed (MR-HIFU), where the MRI is used for treatment planning, and to provide a spatial and temperature feedback to the HIFU during the treatment. In this talk, recent studies on hyperthermia induced drug delivery in tumour bearing rats using MR-HIFU will be presented, employing temperature sensitive liposomes (TSLs). Loading TSLs with a drug and an MRI contrast agents allows monitoring and quantifying the drug delivery with MRI. The challenge is to find TSL systems that stably encapsulate dox and the contrast agent at body temperature, while rapidly releasing both under hyperthermia. The release kinetics of dox and MR agent upon heating is studied *in vitro* and in gel phantoms using MRgHIFU. Biodistribution of the TSLs and dox are assessed in 9L glioma rat model using radiolabeling and dox extraction from tissues. In-vivo studies in tumour bearing rats show that MR-HIFU allows to maintain hyperthermia inside the tumour at T = 42ºC for 30 min. Heated tumours receive about 10−20 times more doxorubicin compared to non-heated tumours. Furthermore, the contrast change observed non-invasively with MRI across the tumour tissue scales with the dose of doxorubicin delivered to the tissue, showing that MRI allows a non-invasive way to visualize the drug delivery process and to quantify the drug dose.

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Polymeric Nanoparticles and Drug Targeting

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Tumour targeting using nanoparticles has been in the forefront of academic and pharmaceutical research for the last several decades. Both passive (enhanced permeation and retention based) and active (ligand based) targeting technologies have been explored and tested on a number of preclinical models. Polymeric nanoparticles have been employed in a number of these studies due to the fact that polymers can encapsulate a variety of actives and the nanoparticles can be functionalized using well developed chemistry methods. Till date, the success of targeting and achieving efficacy in clinical outcomes is very scarce although several human trials have been initiated recently. Needless to say, translation of efficacy from a xenograft or orthotopic animal model to demonstration in human clinical trials is the significant bottleneck to bring out novel therapies. Our approach to targeting has been to test the potentials of nanotechnologies that use polymers for encapsulation and sustained release using pipeline molecules that already partitions to a good degree in solid tumours as evidenced in human clinical trials via oral administration. The objective would also be to be understand if adding a ligand would aid the receptor mediated endocytosis process towards achieving higher local concentrations of the active inside the tumour. Polymeric nanoparticles can act as local depot in the tumour tissues and can enable controlled release at the local acidic pH. Imaging of the nanoparticles − with various size and degree of PEGylation − was utilized to determine their ability to reach target organs and circulation through non tumored rodent via tail vein injection. Data generated using a variety of polymeric nanoparticles such as polystyrene, PLG A, and a cross-linked diblock polymeric nanoparticles would be shared.

Special Session (Sat, 24 Sep, 14:15−15:15)
Peritoneal Surface Oncology − The Evidence for Locoregional Treatment

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Peritoneal Carcinomatosis of Colorectal Origin

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Peritoneal carcinomatosis (PC) is a common event in the natural history of colorectal cancer, presenting as synchronous disease in 5−11% of cases and as metachronous disease in 20−50% of the cases. In the past, carcinomatosis from colorectal cancer has been regarded as a terminal disease. The progress of chemotherapy and biological agents has led to substantial improvement in outcomes, but without long-term survival. Another promising therapeutic option is cytoreductive surgery (CRS) with hyperthermic intra-peritoneal chemotherapy (HIPEC) which gives a median survival of 30−60 months for patients in whom complete cytoreduction is achieved, with 11−30% of patients alive at 5 years. These results were reported by groups using the combination of a comprehensive cytoreductive surgery to treat macroscopic disease with perioperative intraperitoneal chemotherapy to treat microscopic disease. Mitomicin and oxaliplatin (ox) are the most commonly used agents for HIPEC in colorectal cancer. Substantial results in survival have been obtained with these drugs associated to systemic 5-FU or in association with irinotecan, with a median overall survival reaching up to 60 months (ox) after complete cytoreductive surgery. From then on, surgical results are fairly acceptable as well, ranging from 20 to 50% grade III & IV postoperative morbidity rate and 2 to 5% mortality rate. Considering the survival benefit obtained in this situation, morbidity rates should no longer be considered sufficient reason for not using the CRS+HIPEC approach. However, the exact effects of each steps of this combined procedure are currently unknown. The proper role of the

cytoreductive surgery alone was not defined. Similarly, the real impact of HIPEC per se to cure the non-visible microscopic tumour disease has yet to be determined. An ongoing randomized trial comparing HIPEC with no HIPEC after complete CRS (PRODIGE 7) will try and confirm the benefit of intraperitoneal chemotherapy after complete CRS. Considering the encouraging survival results obtained in the treatment of PC by CRS and HIPEC, one of the future indications of this specific approach might be its use in the very early development of PC. Early PC detection is very difficult and can only be ascertained during second look laparotomy. An ongoing trial (PROPHYLOCHIP) is currently comparing the benefits of this second look strategy with HIPEC to the usual simple survey in patients considered at risk of developing a PC.

30 INVITED

Peritoneal Mesothelioma

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Background: Peritoneal Mesotheliomas (PM) represent 10 to 30% of all Mesotheliomas. Diffuse Malignant Peritoneal Mesothelioma (DMPM) is the most frequent form while Well Differentiated Papillary Peritoneal Mesothelioma (WDPPM) and Multicystic Peritoneal Mesothelioma (MCMP) are very rare. With 9 to 15 months median survival, in historical case-series treated with standard therapy, DMPM is considered a lethal condition. Recently, few specialized centers have developed an innovative treatment consisting on Cytoreductive Surgery (CRS) that means a radical resection of the neoplasm associated with Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Furthermore, we focused on new prognostic biomarkers as well as novel terapeutic targets identification.
Materials and Methods: From our data base we selected 134 patients with PM treated with CRS and HIPEC; from these patients, 115 were affected by DMPM and 19 with WDPPM or MCPM. To achieve a radical resection, a complete parietal peritonectomy with a median of 3 visceral resections were carried out. The HIPEC was performed with the closed abdmen technique with cisplatin (42.5 mg/L of perfusate) and doxorubicin (15 mg/L of perfusate) for 90 minutes at a temperature of 42.5ºC. Patients with DMPM received also neo adjuvant or adjuvant systemic chemotherapy. Telomerase Activity (TA), survivin and other members of the inhibitors of apoptosis proteins (IAP) family expression and tyrosin kinases (TKR) and their downstream effectors were studied.
Results: DMPM median survival grew from 12 months with the traditional treatment to 53 months with CRS + HIPEC + sCT with 50% 5 years overall survival (OS). Prognostic factors were: the epithelial subtype compared with the biphasic or sarcomatoid, the absence of lymph node metastasis, the radical surgery and the treatment with HIPEC. The WDPPM or MCPM 5-year OS and progression free survivals were 90% and 79%, respectively. Quality of life is satisfactory since 94% of patients have a resolution of ascites and related morbility and mortality acceptable with reasonable financial cost effectiveness. The TA resulted as a new biologic prognostic factor; while Survivin and other members of the inhibitors of apoptosis proteins (IAP) family as well as TKR and their downstream were overexpressed resulting potential target for targeted therapy.
Conclusion: Based on these findings, CRS with HIPEC is recommended as the optimal treatment to treat PM This methodology is now considered as standard treatment for PM.

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Pseudomyxoma Peritonei

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Pseudomyxoma peritonei (PMP) is a rare disease with a reported incidence of one case per million per year, characterized by the accumulation of mucinous ascites and mucinous peritoneal implants. The primary tumour in the vast majority of cases is a ruptured mucinous appendiceal neoplasm, although this might not be readily apparent. Exceptionally, PMP cases originating from a urachal mucinous tumour, ovarian teratoma or colon neoplasm have been reported.
PMP constitutes the perfect example of a peritoneal neoplastic disease that will only exceptionally metastasize outside of the peritoneal cavity. This peculiar biological behaviour and its slow progress over time make PMP a disease model in Peritoneal Surface Oncology, as it exemplifies the disease status that is amenable to a radical loco-regional therapy.
PMP has certainly played a key role in the development of cytoreductive surgery (CRS) combined with perioperative intraperitoneal chemotherapy (PIC) for peritoneal surface malignancies. Lessons learnt from the radical treatment of this disease have been successfully applied to selected cases of peritoneal carcinomatosis of colorectal or gastric origin, peritoneal mesothelioma or stage III ovarian cancer. These lessons include, among many more, early detection and treatment, multidisciplinary management and centralization in expert treatment centers.
Key prognostic issues in the management of PMP include histopathological grading of the disease and the completeness of cytoreduction, along with patient selection and team experience. Systemic chemotherapy on its own is not a treatment option in this disease except for palliative cases and/or as an adjuvant to complete CRS and PIC in high grade disease.
The scientific justification for the recognition of CRS and PIC as the standard of care for PMP will never come from randomized clinical trials, but it is well-based in the results of numerous phase II studies, some of them including hundreds of patients, that compare very favourably with those of historical controls treated with serial debulking. We must learn to admit that this will be the best possible evidence, and therefore sufficient to offer this treatment to patients. An ambitious international PMP registry project is underway, assembled and coordinated from the Peritoneal Surface Malignancy Program at St. George's Hospital in Sydney, Australia, which will certainly make another invaluable contribution to the knowledge of this disease and its treatment.

Special Session (Sat, 24 Sep, 14:15−15:15)
The Management of Penile Cancer

32 INVITED

Update in Penile Cancer: Facts

Abstract not received

33 INVITED

Surgery in Penile Carcinoma

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Introduction: Partial or radical penectomy are the surgical treatment for invasive penile carcinoma. Both achieve good local control. However these procedures are associated with significant psychosexual morbidity. Interest has therefore been in organ preserving procedures. Inguinal lymphadenectomy (ILND) is the standard procedure to control inguinal lymph-nodes but there is a great controversy regarding to the extent and the timing to perform it.
Material and Methods: The incidence of penile carcinoma is very low and there are no randomized trials available comparing different therapy approaches. The vast majority are retrospective or small prospective case series making impossible to obtain a high level of evidence. The literature was reviewed from 2000 to 2010.
Results: New information suggests that only negative margins instead of 2 cm might be adequate for localized penile tumour, encouraging the use of more conservative therapy strategies. Although local recurrence rate is greater after conservative therapies than amputative surgery, the increase does not seem to have had a negative effect on survival. Quality of life is superior in conservative therapies; however a psychological support is advisable for these patients. In selected patients after penectomy, penile reconstruction should be considered.
In patients with palpable nodes and positive percutaneous biopsy, a bilateral ILND should be performed. In cases of non palpable nodes, the probability of inguinal micrometastases can be estimated using risk groups stratification or nomograms. Surveillance is advisable in low and intermediate risk group with no lymphovascular invasion. Those patients have to complete regular follow-up. In intermediate risk group and motivated high risk patients, dynamic sentinel node biopsy should be recommended, especially in centers where this technology and expertise are available. In cases of positive biopsy, bilateral radical ILND should be performed and surveillance in case of negative biopsy. Modern modify ILND with frozen section is another option for these patients and if positive biopsies, ILND should be enlarged to radical template. In cases of 2 positive nodes, extracapsular extension, grade 3 or positive Cloquet node, pelvic LND should be performed. When fixed inguinal nodes or pelvic nodes are identified in imaging evaluation, induction chemotherapy should be administered followed by rescue LND. Endoscopic LND is a promising new approach in order to decrease LND morbidity but additional studies are required.
Conclusions: Although levels of evidence are low, penile preservation strategies can be considered a safe procedure and more selective LDN indications can be outlined.