IPILIMUMAB (YERVOY) TREATMENT FOR ADVANCED, REFRACTORY MELANOMA: A REPORT OF THE ISRAELI COHORT OF EXTENDED ACCESS PROGRAM

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Introduction: Ipilimumab (Yervoy, BMS) is a monoclonal antibody which antagonizes cytotoxic T lymphocyte antigen (CTLA)-4, a negative regulator of the immune system. Two phase 3 trials have recently demonstrated improved survival of metastatic melanoma patients treated with Ipilimumab. These results have led to the recent approval of Ipilimumab by the FDA for the treatment of metastatic melanoma as well as to the inclusion of Ipilimumab in the Israeli health basket of 2012. Yet, treatment may challenging due to it's unique toxicity profile. Herein we report on safety and preliminary efficacy results of advanced refractory melanoma patients treated on an ongoing compassionate-use program of ipilimumab at Sheba and Hadassah medical center.

Patients / Methods: Patients with advanced refractory melanoma were treated on an international, multi center, compassionate-use program with ipilimumab 3 mg/kg every three weeks for four doses. Patients with evidence of clinical benefit at Week 12 (either complete or partial response or stable disease), were eligible for re-induction treatment upon progression.

Results: Between 4/2010 and 9/2011 148 patients were treated. All patients had at least one prior treatment line for metastatic disease (range 1-5). 109 patients (74%) had M1c disease. 50 patients (34%) had brain metastasis and 47% had LDH above upper normal limits, reflecting poor prognostic characteristics of this cohort. Patients received 3.6 doses of Ipilimumab on average. Treatment was stopped due to completion of treatment plan in 93 patients (63%), toxicity in 18 (12%) and early disease progression in 37(25%). Grade 3/4 immune-related adverse events (irAEs) were noted in 16% of patients, with the most common all grades toxicity being rash (19%), diarrhea (19%) pruritus (13%) and hepatitis (6%). Grade 5 toxicity was noted in 3 patients (2%). 25 patients (17%) required steroid treatment due to toxicity and 5 patients were treated with anti TNF antibodies (Infliximab). Objective response have been noted in 5% (2 with CR, 7 with PR). Another 25 patients (17%) had stable disease, overall yielding clinical benefit in 22%. Median overall survival (OS) was 9 months.

Conclusions: Our results reflect rapid adoption of a new modality of treatment for an unmet need, with manageable toxicity profile and clinical benefit in 22% of patients with advanced, refractory melanoma.

PERITONEAL CARCINOMATOSIS TREATMENT COMBINING RADICAL CYTOREDUCTIVE SURGERY AND NORMOTHERMIC INTRAPERITONEAL CHEMOTHERAPY: RESULTS OF THE TREATMENT OF 30 CASES

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Background: The treatment of Peritoneal Carcinomatosis (PC), whether primary or secondary, remains a challenge for surgical oncologists. PC is treated for more than two decades with good results by a combined aggressive cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC), mostly hyperthermic (HIPEC). Few reports deal with normothermic IPC (NIPC).
Methods: A restrospective review of PC patients charts after CRS with IPC procedures treated at our institution. Demographic, clinical, operative and post-operative, histological and follow-up data were retrieved. All the data were statistically analyzed (SPSS 18.0) for impact on survival.
Results: Between 2001 and 2010 44 PC patients underwent 50 CRS and IPC procedures. In this work were included 30 PC patients who received normothermic IPC after CRS. A majority of 20 females (66.7%) with a mean Karnofsky Score of 85%. Most patients (24/76.6%) had a Peritoneal Carcinomatosis Index (PCI) over 10 (range 0-39), Completeness of Cyroreduction Score (CCS) of 0-1 respectively for 15 and 10 patients. PC histology: 10 colorectal, 10 appendix, 4 papillary serous PC, 3 mesotheliomas and others. Two cases with post NIPC neutropenia and one fatal post-operative pulmonary embolus (3.33%). Median survival overall is 23.5 months (range 1-152), PC from CRC origin 19 months, appendix origin 56.6 months (p=0.045). In a multivariate analysis patients born in former USSR had a shorter survival (p=0.017).
Conclusions: This CRS and NIPC report shows survival results (overall, appendiceal and colorectal PC) similar to reports of CRS with HIPEC, and the morbidity and mortality rates compares fairly. This should emphasize the need for a randomized trial comparing HIPEC and NIPC after similar CRS efforts.

MALIGNANT LESIONS OF THE ADRENAL GLAND - CAN BE SAFELY RESECTED LAPAROSCOPICALLY!

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Introduction: The main concern when surgically approaching adrenal lesions is the peritoneal spread of malignant tumors. Laparoscopic Adrenalectomy (LA) is the treatment of choice for benign adrenal lesions. Size of the lesion and radiologic features define the risk for malignancy. In lesions with high such risk the experience with the laparoscopic approach is limited and therefore controversial. The purpose of this study is to determine the feasibility and oncological safety of LA for malignant disease.
Methods: Retrospective analysis of prospectively collected database. All adrenalectomies performed in our department between 2003-2011 were reviewed and demographic, perioperative and follow up data for those who had malignancy in the final histological report was analyzed. Data is presented as mean (range).
Results: Out of 121 adrenalectomies we identified 20 patients with 21 malignant adrenal pathologies: 11 primary tumors; 5 Adreno Cortical Carcinoma; 5 Large B cell Lymphoma; 1 Leomyosarcoma; 10 Metastatic lesions included 5 Malignanat Melanoma (1 Patient- both sides); 4 Adeno-Carcinoma and 1 Leomyosarcoma. All operations were performed laparoscopically. Mean tumor size was 7 (5-9)cm, operative duration was 70 (45-145)min, estimated blood loss was 80 (20-500)cc. All patients resumed regular diet on POD 1 and mean length of stay was 2.4 days. 2 patients died 6 & 24 months post operatively. 2 patients were lost to follow up. All the rest of the patients are alive and well with mean follow up of 46 (7-96) months.
Conclusions: LA for primary or metastatic malignant lesions is feasible and oncologically safe. Surgical principles should be the same for all adrenalectomies: Enbloc resection of all epinephric fat, minimal touch technique and low threshold for conversion. Size alone should not be an indication for open surgery.

MULTIDISCIPLINARY MANAGEMENT OF VERY ADVANCED STAGE III AND STAGE IV MELANOMA: A PROOF OF PRINCIPLE

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Introduction: Potentially resectable advanced Stage III and Stage IV melanoma is a selected subgroup that gains maximal advantage if being treated in a Melanoma Center. Surgery combined with chemo/chemo-bio therapy may yield durable remissions and long term palliations.
Methods: Prospectively non-randomly selected 37 patients underwent systemic therapy with a plan of consolidating the treatment by surgery. Data were collected prospectively, and analyzed retrospectively. Median follow-up from diagnosis was 50 (3-307) months, and 15 (1-156) months when calculated from last intervention.
Results: 22 males and 15 females, median age at diagnosis 44 (20-71) years, 13-trunk, 13-extremity, 3-H&N and 8 unknown primary melanomas were included. There were 17 Stage III and 20 Stage IV pts. With median Breslow 3.7 (0.45-26) mm. Chemo/chemo biotherapy achieved 7 cCRs, 28 PRs and 2 Stable Disease. 6 of the 7 cCRs were operated on, securing pCR in 5 and PR in one. 4 of these 5 and the PR patient are still NED. 21 of 30 PR's were rendered NED by surgery; 14 of these 21 died of melanoma, one is alive with stable disease. Overall, 11 of 37 patients have not died of melanoma median of 72 (14-156) months after last intervention. Of the 8 patients with unknown primary, 5 have not died of melanoma median of 89 (30-156) months after last intervention.
Conclusion: Patients with marginally resectable Stage III and Stage IV melanoma have a significant 30% chance, according to this series, for durable remission if treated by a multidisciplinary team in a melanoma center using induction chemo biotherapy and surgery. Results seem even more favorable for patients with an unknown primary lesion. In view of the new effective treatments for melanoma approved this year, this series may be considered a proof of principle, enabling long term remissions by combining induction therapy and surgery.

INITIAL EXPERIENCE IN MAINTAINING SYSTEMIC NORMOTHERMIA IN PATIENTS UNDERGOING HIPEC USING A NOVEL THERMOREGULATION DEVICE

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Introduction: Cytoreductive surgery (CRS) and Hyperthermic Intra Peritoneal Hyperthermic Chemotherapy (HIPEC) are associated with major physiologic changes in the patient's homeostasis. Core body temperature (CBT) may shift from hypothermic conditions due to the prolonged duration of the open abdomen and blood loss, into hyperthermia caused by the perfusion of heated chemotherapy. Temperature shift may result in increased risk for post operative complications and as a result prolong hospital stay.
Methods: This feasibility study with undertaken with a main aim to test a novel thermoregulation device (CritiCool®, MTRE, Yavne, Israel), currently used for maintaining hypothermia in patients following cardio-pulmonary resuscitation, for decreasing temperature shifts in patients undergoing CRS+HIPEC. Patients undergoing CRS+HIPEC were included. Real-time CBT was measured in all patients. CBT of Patients treated by forced air warming **(**Bair Hugger® Eden Prairie, MN, USA= Group A) was compared to patients undergoing thermoregulation using CritiCool® (= Group B). In Group A, forced air warming was stopped one hour before perfusion and the CBT was allowed to drop to 35°C, while in Group B, CBT was maintained at 36°C by shifting to a "cooling mode" one hour before perfusion.
Results: The HIPEC database was searched and out of 75 patients who underwent CRS+HIPEC by our group, there were complete datasets of real-time temperature recordings in 30 patients. Patients were divided into the two study groups, according to the thermoregulation device used at the time of surgery, resulting in 25 patients in Group A and 5 patients in Group B. Mean CBT temperature at the beginning of the perfusion was 36.2°C (range 34.9°C-38.3°C) and 36.2°C (range 35.5°C-36.7°C) in Groups A and B, respectively. Mean CBT temperature at the end of the perfusion was 38.4°C (range 37.9°C-39.5°C) and 36.2°C (range 35.8°C-36.7°C) in Groups A and B, respectively (p=0.001). There was no difference in mean temperature of the perfusate, adjacent tissues (urinary bladder probe) between the two groups.
Conclusions: Shits in CBT during HIPEC can be decreased significantly using a novel thermoregulation device without losing the efficacy of the HIPEC as measured in the tissues surrounding the peritoneal cavity.

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN): MIRNA MOLECULAR PROFILING OF INDIVIDUALS AT HIGH RISK FOR MALIGNANCY

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Introduction: Intraductal papillary mucinous neoplasms (IPMN) represent a spectrum of tumors that range from low grade dysplastic tumors to invasive cancer. Preoperative identification of malignant IPMN is important, as it would allow for true selection of patients most likely to benefit from surgical resection. MicroRNAs (miRNAs) are small endogenous noncoding RNAs which post-transcriptionally regulate gene expression and have been implicated in carcinogenesis. Our aim was to evaluate whether miRNAs are differentially expressed between low grade and malignant IPMN.

Methods: All IPMN resected between 1995 and 2011 were reviewed by two GI pathologists. Forty five patients with pathologically confirmed IPMN were included. Samples were grouped into low risk (low grade dysplasia, moderate grade dysplasia, n=15) and high risk categories (high grade dysplasia, n=10; carcinoma, n=10; or low grade dysplasia microscopically dissected from malignant IPMN, n=10). 846 human miRNAs were profiled and cancer related differentially expressed miRNAs were validated using quantitative real time-PCR (qRT-PCR).

Results: Hierarchical clustering demonstrated grouping of two main IPMN sub-groups: low grade versus high grade IPMN and carcinoma. We found that 24 miRNAs were differentially expressed (14 upregulated, 10 downregulated) in high grade IPMN and carcinoma compared to low grade IPMN ($p<0.05$). The expression of representing cancer related miRNAs (miR-21, miR-155, and miR-217) significantly differ between clusters (2 fold increase/decrease; $p<0.05$) and these were validated using quantitative RT-PCR showing that the expression of these specific miRNAs is associated with IPMN tumour aggressiveness. Interestingly, miR-155 expression level (in addition to other cancer associated miRNAs) and IPMN grade were directly proportional. Moreover, low grade IPMN samples that were dissected from tumors harboring remote carcinoma significantly differ from low grade IPMN and were also clustered in the high risk category.

Conclusions: This study shows that miRNA expression patterns of low grade IPMN are different from malignant IPMN. Moreover, it demonstrates that cancer related miRNAs, i.e. miRNA-155, are specifically expressed in direct proportion to IPMN aggressiveness. This association indicates their biological relevance and highlights their potential for development as clinically significant biomarkers to better stratify high risk IPMN patients to surgery.

EPITHELIAL-MESENCHYMAL TRANSITION MOLECULAR BIOMARKERS IN MALIGNANT INTRADUCTAL PAPILLARY NEOPLASM (IPMN)

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Introduction:. Epithelial to mesenchymal transition (EMT) is a biological process that allows well-differentiated, polarized epithelial cells to undergo a conversion to motile, unpolarized mesenchymal cells. EMT plays a key role in cancer invasion, metastasis, and drug resistance; thus, frequently associated with increased tumor aggressiveness and poor prognosis. We evaluated EMT involvement in IPMN tumorigenesis and whether selected EMT biomarkers are differentially expressed between low grade and malignant IPMN.

Methods: All IPMN resected between 1995 and 2011 were reviewed by two GI pathologists. Thirty five patients with pathologically confirmed IPMN were included. Samples were grouped into low risk (low grade dysplasia, moderate grade dysplasia, n=15) and high risk categories (high grade dysplasia, n=10; carcinoma, n=10); 846 human miRNAs were profiled and EMT related differentially expressed miRNAs were validated using quantitative real time-PCR (qRT-PCR).Twenty seven representing normal and IPMN paraffin embeded samples were immunohistochemically stained for E-Cadherin and Vimentin; these were scored by a GI pathologist.

Results: Hierarchical clustering demonstrated grouping of two main IPMN sub-groups: low grade versus high grade IPMN and carcinoma. We found that 24 miRNAs were differentially expressed
(14 upregulated, 10 downregulated) in high grade IPMN
and carcinoma compared to low grade IPMN ($p<0.05$). The expression of previously reported EMT regulatory miRNAs significantly differ between clusters: miR- 200a,c were down regulated (2 fold decrease) in malignant IPMN as compared to low grade IPMN ($p<0.05$); consistent with the known role for the miR-200 family in negatively regulating EMT. MiR-141, also known to play a role in EMT, was down regulated (1.8 decrease) in high risk IPMN ($p<0.05$). These miRNAs were validated using quantitative RT- PCR. E-cadhein expression, which is directly regulated by the miR-200 family was significantly lower in high grade IPMN and carcinoma versus low grade IPMN ($p<0.05$). On the contrary, vimentin expression was increased in high risk IPMN samples ($p<0.05$).

Conclusions: To the best of our knowledge this is the first study reporting EMT features in malignant IPMN. These data indicate that miR-200a,c as well as miR-141 may play a role in IPMN biology; these could be utilized as potential novel biomarkers identifying high risk IPMN patients most likely to benefit from surgery.

PERIOPERATIVE BETA-ADRENERGIC BLOCKER AND A COX-2 INHIBITOR IMPROVE CANCER RALATED SURVIVAL. RESULTS OF AN ANIMAL MODEL AND OUTLINE OF A CLNICAL TRIAL IN COLORECTAL CANCER

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Background: Resection of the primary tumor is imperative in the treatment of colon and rectal cancer. However, surgery by itself induce physiological changes resulting in significant immune depression and other physiological perturbations, which may play a significant role in the initiation of new metastases and the progression of pre-existing dormant metastases. Our group has recently implicated that postoperative stress related immunosuppression is mediated by excess perioperative secretion of catecholamines (CAs) and prostaglandins (PGs). Based on these results, we have developed treatment using a CAs antagonist combined with a COX2 inhibitor, which attenuated stress induced immunosuppression and reduced metastatic load in cancer animal models, including colon cancer.
Methods: Animal survival model using syngeneic models of spontaneous metastasis following tumor excision was performed. Mice were injected with B16 melanoma or Lewis lung carcinoma cells to the footpad. Once a developing tumor, the mice underwent drug treatment with placebo, propranolol, etodolac, or the combination of propranolol and etodolac, and the tumor was excised. Long-term survival rates were assessed thereafter.
Results: The combined therapy significantly increased survival rates in animal models compared to each treatment alone or placebo. There was no significant difference in survival between treatment with each of the drugs alone and placebo.
Discussion: The results of this animal survival study suggest that the combined treatment with CAs antagonist and COX2 inhibitor may be effective in prevention of development of distant metastasis. The COMPIT (Colorectal Metastasis Prevention Israeli Trial) is an ongoing phase 2 double blind placebo controlled clinical trial aimed to assess the perioperative use of propranolol and etodolac on tumor recurrence and immune parameters in colorectal cancer patients. Patients undergoing resection of non-metastatic colon and rectal cancer will be randomly assigned to perioperative treatment with etodolac and propranolol or placebo for an intervention phase of 20 days. Follow up for cancer recurrence will include semi-annual follow up for 3 years. Blood samples will be assessed for immunological and endocrine testing.

PANCREATICODUODENECTOMY IN THE ELDERLY: IS IT JUSTIFIED IN TERMS OF MORTALITY, LONG TERM MORBIDITY AND QUALITY OF LIFE?

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Introduction: Pancreaticoduodenectomy (PD) in the elderly is gaining acceptance and being performed in increasing numbers for malignant and pre-malignant pathologies. Several reports demonstrate acceptable early postoperative outcome and modest long term oncologic results, yet data analysis of quality of life in this particular population is lacking. We evaluated long term morbidity, mortality, and residual quality of life after PD in the elderly.

Methods: A prospectively accrued pancreatic surgery database was analyzed for postoperative complications and mortality (30 and 60 days), ICU, hospital and rehabilitation facility stay, as well as readmissions during the first year after surgery. Quality of life (QOL) was assessed by a validated questionnaire in three domains: physical, psychological, and social (EORTC QLQ-30) 3-6 and 12 months after surgery. Scores are reported as a percentile, with 100% being the highest possible score.

Results: One hundred seventy-two patients aged ≥ 70 years had PD at our institution between 1995 and 2010, the majority for ductal adenocarcinoma (61%; n=105); most patients (72%; n=124) were categorized as ASA ≥ 3. There was no intra-operative death, 30- and 60-day postoperative mortality rates were 6.4% vs. 7.5%, respectively (p=0.23). Median intensive care unit and general hospital stay were 2 days (range, 0-16) and 22 days (range, 8-63), respectively. Sixty-four patients (37.5%) were discharged to a rehabilitation facility where their median length of stay was 8 days (range, 4-45). Hospital re-admission during the first year was documented in 54 patients (31%); of them, 75% were admitted once. Median follow-up length for the entire cohort was 22 months (range, 1-187), one- and 2- year overall survival (OS) rates among cancer patients were 58% (SE: 3.1) and 36% (SE: 3.6), respectively. Overall quality of life (QOL) scores 3 and 12 months after surgery for the 51 responding PD patients were 68%, and 73%, respectively. These scores were lower, yet comparable to those of 20 matched laparoscopic cholecystectomy patients.

Conclusions: Most elderly cancer patients survive longer than one year after PD, more than a third longer than two years. These patients are likely to have an acceptable long term morbidity and overall good QOL, corresponding with their age. These data should discourage the ongoing trend to avoid PD in the elderly.