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CANCER INSIGHTS News From UPMC CancerCenter

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MEDICAL ONCOLOGY
Edward Chu, MD

Evaluating the scenarios and treatment options for metastatic colon cancer.

Page 2

RADIATION ONCOLOGY
Dwight Heron, MD, FACRO

Highlighting a neuro-oncology patient on the Aposense trial.

Page 5

SURGICAL ONCOLOGY
David Bartlett, MD

Evaluating the surgical treatment of a patient with peritoneal mesothelioma.

Page 8

At the University of Pittsburgh Cancer Institute and UPMC CancerCenter, we realize living with cancer requires vigilance, determination, and more than a little fight on the part of our patients, which is why our physician-scientists and clinicians continue to seek new ways to understand, diagnose, and treat this disease.

As physicians and researchers, we realize that the latest cancer research makes the most impact when it touches a patient, which is why our commitment to patients and their families continues to inspire us in the lab to seek the next breakthrough in cancer medicine.

This edition of Cancer Insights features three case studies that highlight some of our most promising research and clinical trials. The first case study compares cytotoxic chemotherapy regimens and the role of anti-EGFR antibody therapy in treating patients with metastatic colorectal cancer. The second case study discusses how the measurement of tumor apoptosis could predict response to stereotacticradiosurgery. The third case study considers the therapeutic options for the management of malignant peritoneal mesothelioma and recommendations regarding standard of care.

We have given Cancer Insights a sleek new look that allows you to meet the physician-scientists leading these initiatives. The addition of case studies also gives you the option of earning Continuing Medical Education credit after you have used the resources available in our new digital format or read Cancer Insights.

I hope you will find Cancer Insights to be a useful tool in your day-to-day practice. To learn more about clinical research or patient care opportunities at UPCI and UPMC CancerCenter, please call 412-647-2811 or visit our website at UPMCCancerCenter.com.

Sincerely,

Nancy E. Davidson

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Disclosures: Doctors Chu, Heron, Clump, Mintz, Bartlett, and Choudry have reported no relationships with proprietary entities producing health care goods or services.

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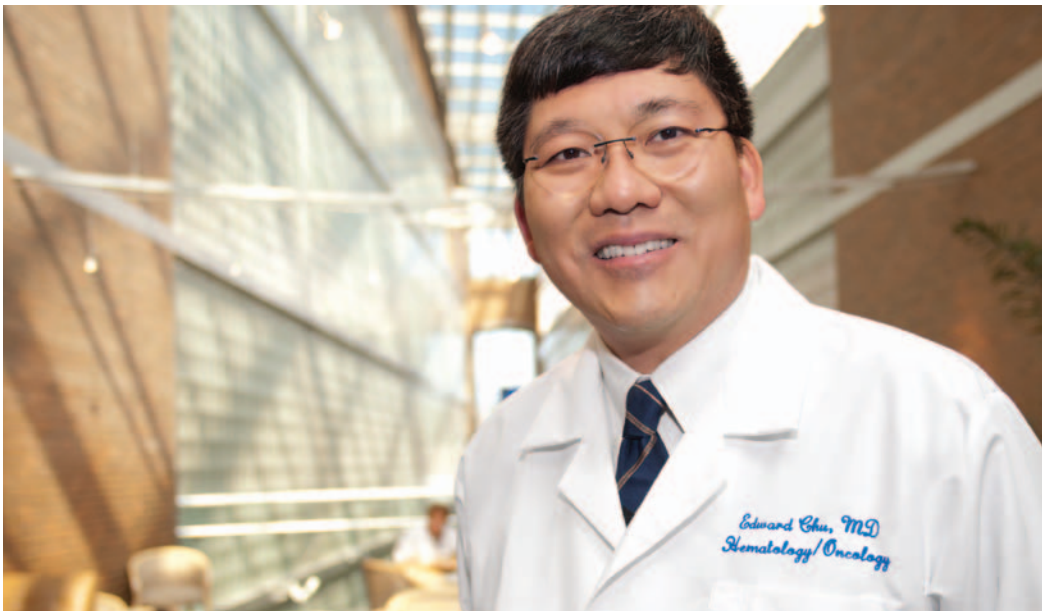


MEDICAL ONCOLOGY

Case Study: Patient With Metastatic Colorectal Cancer

Edward Chu, MD

Chief, Division of Hematology-Oncology
Deputy Director, UPCI

Patient profile:

- 58-year-old male presents with metastatic colorectal cancer with multiple (>6) small lesions throughout both lobes of the liver
- History of hypertension and AODM, which are both under good control
- CrCl is 30 mL/min, presumably secondary to hypertension and AODM
- No previous history of chemotherapy
- No prior history of bleeding or arterio-embolic events
- Feels well, has no tumor-related symptoms, and has an ECOG PS of 0
- Serum chemistries and CBC are normal
- CEA 125 ng/mL, alk phosph 220, LDH 350, and serum bilirubin 2.0
- Assessment of tumor reveals KRAS mutation

The salient features in this case include: the patient is asymptomatic; has a good performance status (PS); has what was felt to be surgically unresectable, liver-limited disease; and genotyping of his tumor shows him to have KRAS mutation.

In considering potential treatment options for this patient, the first decision point is to consider what type of chemotherapy he should receive. My choice for this individual would be to use a cytotoxic combination drug regimen, as opposed to fluoropyrimidine monotherapy, given his good performance status.[1] Moreover, while he was felt to be surgically unresectable upon initial evaluation, one of the main goals of our treatment strategy would be to see if his liver-limited disease can, in fact, be cytoreduced to the point where the surgical oncologist feels confident that surgical resection is possible.

Discussion

In this regard, the potential choices would be oxaliplatin- or irinotecan-based chemotherapy.[2,3] It is interesting to note that up to 80-90% of patients in the United States are treated with oxaliplatin-based chemotherapy in the front-line setting. However, when the clinical data are critically evaluated, it is clear that the clinical activity of FOLFOX and FOLFIRI is equivalent in terms of overall response rate (RR), time to tumor progression (TTP), and overall survival (OS).[4,5] As such, they should be viewed as equivalent treatment options in the first-line setting. Both regimens are well-tolerated with manageable safety profiles. However, given the different spectrum of toxicity with each regimen, with peripheral sensory neuropathy being a significant issue with oxaliplatin, and GI toxicity being potentially dose-limiting in patients with irinotecan, choices

can be appropriately made as to which type of toxicity a patient is willing to experience.

There are several reasons that I would not favor irinotecan for this particular patient. The first is that his serum LDH and bilirubin are elevated. The clinical data generated, to date, suggest that in this clinical setting, patients experience an increased risk of GI toxicity, in the form of abdominal pain/cramps and diarrhea.[6,7] The second reason is that irinotecan-based chemotherapy results in a much higher incidence of liver-associated toxicity, as manifested by steatohepatitis, which has been shown to be associated with a greater risk of post-operative surgical complications following liver-directed surgery.[8] Given these concerns, I would favor oxaliplatin-based chemotherapy.

What about the fluoropyrimidine base to be combined with oxaliplatin? The NO16966 trial is the largest randomized phase III clinical trial conducted, to date, and the main goal of this trial was to directly compare the combination of oral capecitabine and oxaliplatin (XELOX) with infusional 5-FU plus oxaliplatin (FOLFOX-4) in the first-line setting.[9] This study clearly demonstrated that XELOX was equivalent to FOLFOX4 in terms of RR, progression-free survival (PFS), and OS. Of note, the incidence of grade 3/4 neutropenia (7% vs. 44%) and febrile neutropenia (1% vs. 5%) was significantly higher in patients treated with FOLFOX-4 chemotherapy when compared to XELOX. In contrast, grade 3/4 GI toxicity in the form of diarrhea as well as neurosensory toxicity were comparable in the two arms. In addition to the NO16966 study, there are several phase 2 trials, and a few underpowered randomized phase 3 trials, all of which confirm the equivalent clinical activity of XELOX and FOLFOX regimens.[10]

While I am a big fan of capecitabine-based regimens, I would not be in favor of using the XELOX regimen in this specific patient. Because of his underlying diabetes and hypertension, he has impaired renal function . Capecitabine and its metabolites are cleared by the kidneys, and in the setting of renal dysfunction, there is an increased risk of drug toxicity. For this reason, capecitabine must be dose-reduced by 25% when the CrCl is 30-50 mL/min and is contraindicated when CrCl<30 mL/min. Because this patient is on the border with a CrCl of 30 mL/min, I would not recommend using capecitabine.

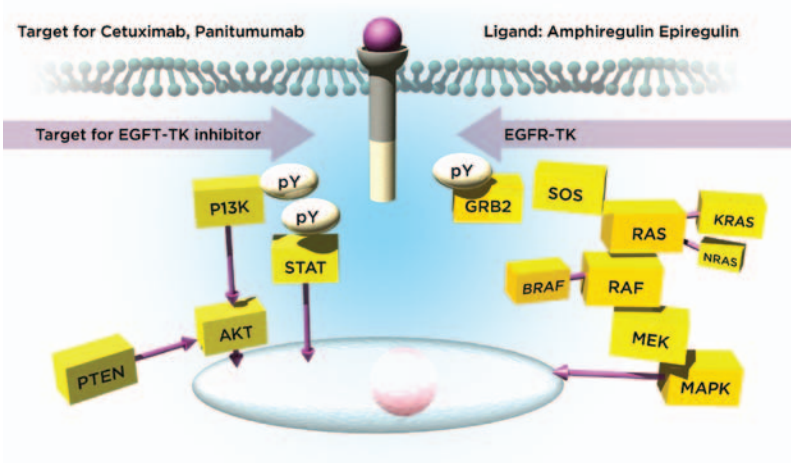
In response to the question about which cytotoxic chemotherapy regimen should be used, I would select FOLFOX. My preference is to delete all bolus injections of 5-FU, to start with an infusional dose of 2,400 mg/mg2 for 46 hours and if tolerated, to increase the dose to 3,000 mg/m2 for 46 hours. I also prefer to use a lower dose of leucovorin at 20 mg/m2, as opposed to the higher doses of 200 mg/m2 or 400 mg/m2 of leucovorin that are typically used with the various FOLFOX regimens.

The second question refers to the biological agent that should be combined with cytotoxic chemotherapy. Given that the patient's tumor was found to be mutant KRAS, the chances that cetuximab or panitumumab would have clinical activity would be extremely low. As a result, I would use the anti-VEGF antibody, bevacizumab, which has been shown to provide clinical benefit when combined with 5-FU-, capecitabine-, irinotecan-, and oxaliplatin-based chemotherapy regimens.[11,16] There is no clear role for the dual biologic antibody approach of bevacizumab and cetuximab/panitumumab, even in the setting of wild-type KRAS mutations. Moreover, there is convincing data that the clinical outcomes are significantly worse when patients with KRAS mutations are treated with the dual antibody approach.[17,18]

Even in responsive patients, the duration of bevacizumab effectiveness is limited. It had been widely assumed that drug resistance would not develop to anti-angiogenic treatment approaches. There is now growing evidence that cellular resistance does indeed develop to bevacizumab. One potential mechanism for the emergence of resistance is the activation of alternate signaling pathways that drive angiogenesis. Increased levels of basic fibroblast growth factor (bFGF) were observed in the plasma of mCRC patients treated with bevacizumab prior to the development of disease progression, suggesting that upregulation of this growth factor pathway may represent a mechanism for cellular drug resistance.[19]

The final point to consider relates to the role of KRAS mutational status. It is well-established that mutations in KRAS result in constitutive activation of the RAS-RAF-ERK pathway. Approximately 35%-40% of CRC tumors express mutations in codons 12, 13, and 61 of the KRAS gene.[20] In general, tumors with these mutations are not responsive to EGFR-directed antibody therapy, thus making KRAS status an important predictive biomarker for mCRC. However, a recent analysis of pooled data of 579 patients with chemotherapy-refractory mCRC treated with cetuximab suggests that not all KRAS mutations are equal in their ability to confer resistance to cetuximab therapy. In this study, De Roock and colleagues showed that patients with a Gly13Asp (G13D) mutation in codon 13 derived clinical benefit from cetuximab treatment when compared to those with other KRAS mutations.[21] In addition to its key role as a predictive biomarker, there is growing evidence that KRAS mutations also may provide important prognostic information associated with worse clinical outcomes. At the 2011 ASCO meeting, Tejpar and colleagues reported on the results of a retrospective analysis of the CRYSTAL trial, which provides further evidence that patients with the G13D KRAS mutation derived clinical benefit from cetuximab therapy, in contrast to patients with codon 12 mutations.

Thus, there is now growing evidence that not all KRAS mutations are created equal, and it will be critically important for us, as the practicing clinicians, to know exactly which specific KRAS mutation that has been identified by molecular testing before deciding whether a particular patient is eligible for anti-EGFR antibody therapy.



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Cancer LiveWell Survivorship Program Expands

Magee-Womens Hospital of UPMC recognized a need to support cancer survivors following treatment. In October 2009, Magee implemented the Women's Cancer LiveWell Survivorship Program and began with a single survivor workshop. The program continued to expand as it became more popular with survivors, and now includes clinical services, workshops, education series, support programs, cooking classes, and various other supportive services. Since its inception, the LiveWell Survivorship Center has scheduled more than 170 patient visits, and has welcomed more than 700 survivors to its workshops.

As a result of the program success at Magee, in July 2011, the LiveWell Survivorship Program at Hillman Cancer Center, which serves both male and female survivors, was instituted. The Program is designed to address individual questions and medical issues so survivors can live well-rounded, productive, and fulfilling lives after their cancer diagnosis and treatment. It provides an ideal learning opportunity for cancer survivors or their health care providers who seek specialized expertise on important cancer-survivor-related topics.

Both programs offer oncologists, nurse practitioners, physician assistants, psychologists, psychiatrists, physical therapists, and dietitians for consultative and follow-up care to all cancer survivors who have no metastatic disease and have completed their therapies, or who undergo long-term cancer therapy. The program's providers maintain close contact with the survivors' current health care providers to ensure continuity of care. Cancer survivors also have access to comprehensive and relevant research studies.

To reach the LiveWell Survivorship Program at Magee, please call 412-641-4530, ext. 1.

To reach the LiveWell Survivorship Program at Hillman, please call 412-692-4724.

RADIATION ONCOLOGY

Case Study: Evaluating the efficacy of [18F]-ML-10 as a noninvasive imaging tool for the early detection of response of radiation therapy

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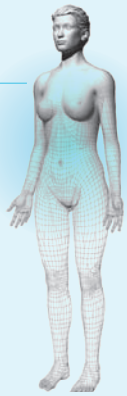
Patient Profile



- A 39-year-old female with a past medical history significant for ovarian cancer, originally diagnosed in June 2008, presented eight months later with a headache and left-sided arm weakness. Upon workup, she was found to have a 2.3 cm right frontal enhancing lesion suspicious for metastatic dissemination. Her symptoms improved with steroids (dexamethasone) and she denied further symptoms.
- On assessment, her Karnofsky performance status (KPS) was 90 and her neurological examination was nonfocal. She was referred to discuss the potential role of radiotherapy in the management of her intracranial metastasis from her ovarian cancer. Based upon her KPS and her limited intracranial disease, stereotactic radiosurgery (SRS) was recommended as the treatment of choice over whole brain radiation therapy (WBRT).
- SRS has been proven to offer excellent local control and fewer neurological sequelae when compared to WBRT.[1] To further assess her intracranial disease and to assist in treatment planning, a thin-slice, high-resolution (1.25 mm) MRI with double dosing of gadolinium was used. Her treatment comprised a single fraction delivered via the CyberKnife™ Robotic Stereotactic Radiosurgery delivery system.

Discussion

Currently, models using clinical variables such as age, performance status, number of intracranial lesions, as well as extent of metastatic and extracranial disease provide the best estimate of prognosis.[2,3] Efficacy of treatment intervention is still commonly assessed using anatomic imaging, such as MRI or CT and serial clinical physical examination. Unfortunately, changes in tumor morphology on imaging that are reflective of an SRS response can be seen after several weeks to several months following completion of radiosurgery. Moreover, during this acute period following SRS there is often an inflammatory response with increased tumor size and edema on MRIs in the first two months. More importantly, in cases where there is no response, the patient is unnecessarily exposed to the treatment's side effects, and precious time may be lost before the initiation of an alternative, potentially more beneficial line of therapy. Clearly, tools that provide both prognostic, and predictive information regarding the response to anti-cancer treatments are therefore urgently needed.

Molecular imaging aims to address this need by providing noninvasive imaging of biological processes rather than anatomy.18F-fluoro-2-deoxyglucose (18F-FDG) is the prototype of such a molecular imaging tool and PET emerges as the leading imaging modality for molecular imaging. There is a growing use of 18F-FDG as both a predictive and prognostic tool in many malignancies.[4] Tumor uptake of 18F-FDG reflects the high rate of metabolic glucose utilization by the dividing tumor cells, and therefore comparison of the ratio of 18F-FDG uptake before and after treatment may reflect the treatment-related reduction in the amount of tumor cell metabolism.

However, it is now recognized that 18F-FDG uptake has several substantial limitations as a surrogate marker for the monitoring of tumor response to treatment. Its use for assessment of treatment response is mainly limited to tumors with a rapid growth rate. Most importantly, its accuracy for assessing treatment response can be affected by tracer uptake by

inflammatory cells and reduced uptake by tumor cells undergoing metabolic stunning, but not cell death.[5] Moreover, for assessment of treatment response in brain tumors, the use of FDG PET is limited by its high background uptake by brain tissue, associated with the normally high metabolic utilization of glucose by brain cells.

Induction of cell death through initiation of apoptosis is the primary mode of action of many anti-cancer treatments. An apoptotic peak is detected in tumors in response to chemotherapy within days and in response to radiation therapy within hours from initiation of treatment.[6] Anti-cancer treatments trigger apoptosis in the tumors by various mechanisms, such as DNA strand breaks, damage to proteins, and inflammatory or ischemic processes. The correlation between apoptosis and tumor response to treatments has been demonstrated in various models in vitro and in vivo. Detection of apoptosis may therefore be beneficial for early, real-time monitoring of tumor response to treatment, and may thus be useful to improve management of the cancer patient.

Radiotherapy is the ideal treatment for intracranial metastases, which are protected from the majority of systemic therapies by the blood/brain barrier. It has the advantages of activity across numerous types of tumors and unquestionable dose-related power in eradication of cancer cells and tumor blood supply, as it causes irreversible and lethal damage to DNA and other cellular macromolecules, which initiates apoptosis, as well as causing damage to the tumor microvasculature. As such, radiation has an important role in the treatment of solid tumor metastases to the brain, with radiation strategies ranging from WBRT to focal modalities, such as SRS.[7]

WBRT is used frequently for large and/or multiple metastases, delivering fractionated radiation for a period of two weeks, exploiting the relatively higher vulnerability of tumor's dividing cells to the radiation damage, compared with the surrounding healthy tissue. These strategies have been reported to achieve at least temporary tumor control in 60% to 80% of the cases. However, WBRT has been associated with concomitant damage to healthy brain tissue, ranging from cerebral edema to brain atrophy and leukoencephalopathy, with associated neurological deficits such as dementia; therefore, focal delivery is desirable.[8]

SRS involves the delivery of high radiation doses to localized lesions with high accuracy, allowing strong anti-tumoral effect, while lessening radiation injury to the surrounding normal tissues. It has been shown that larger doses of radiation given at shorter intervals are more effective than smaller fractions given over a longer period of time. The focal delivery of high-dose radiation to brain metastases has been shown to yield encouraging local tumor control, with a relatively low toxicity. In addition to the direct damage to tumor cells by irradiation, recent evidence suggests that a prominent effect of large-dose single fraction radiation therapy is induction of apoptosis of endothelial cells in tumor microvasculature.[9] This effect impairs tumor microcirculation, causes microvascular collapse, and induces tumor ischemia, thus further contributing to tumor cell damage.

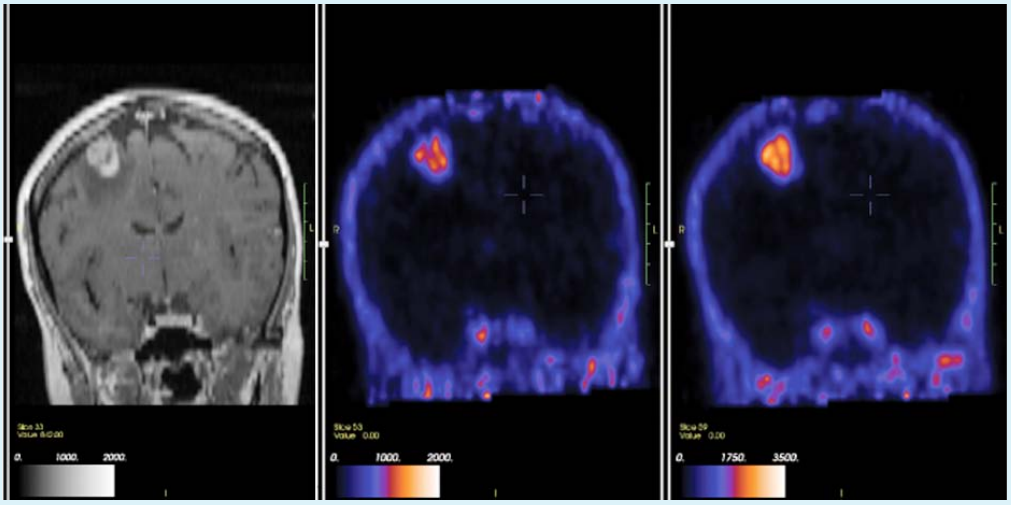
[18F]-ML-10 is a novel, low molecular-weight probe under development for clinical imaging of apoptosis in vivo by PET. [18F]-ML-10 is a member of the ApoSense® family of compounds, a novel class of molecular probes for molecular imaging of apoptosis. In various models in vitro, and in experimental cancer models in vivo, it has been shown that ApoSense compounds can detect apoptotic cells (as well as cells undergoing mitotic catastrophe) encountered in response to various chemotherapeutic and radiation treatments. ML-10 uptake is specific to apoptotic cells, and the compound is excluded from viable cells. Therefore, the compound will not accumulate in areas of inflammation, unless there are associated cells undergoing cell death. [18F]-ML-10 has been examined in two clinical trials and has been found to be safe for administration to healthy subjects and also to elderly subjects with acute ischemic cerebral stroke. In these clinical trials, [18F]-ML-10 also was found efficacious in the clinical imaging of apoptosis, including either the normal physiological process of apoptosis as observed in the testes of young healthy males, or pathological cell death, as observed in the brains of patients with acute ischemic cerebral stroke.

Currently, the University of Pittsburgh Cancer Institute is leading a national effort to evaluate the efficacy of [18F]-ML-10 as a non-invasive imaging tool for the early detection of response of radiation therapy in patients with brain metastases, from epithelial cancer, such as lung, head,

Aposense Study CA004 - Brain Metastases Treated by SRS MRI and [18F]-ML-10 PET Images

Note: More intense signal change.

Figure 1 on 1-24 hour scan indicating greater degree of apoptosis in the treated tumor.



Baseline MRI

Baseline ML 10
130-150min post-injection

Follow-up ML 10 ~ 24 hours Post SRS
130-150min post-injection

and neck cancers. The previously described patient consented for enrollment on the ApoSense study. Based on the size of the lesion in the right frontal lobe, a dose of 18.0 Gy to the 80% isodose line or a max dose of 22.5 Gy was prescribed. Figure 1 demonstrates the ML-10 change in uptake in a patient treated on the ApoSense trial (UPCI # 08-129). It is felt that this study will enable the early detection of tumor response and subsequently improve clinical management of these patients. Additionally, it may enable early identification of non-responders, and subsequently potentially lead to refinement of radiation dose, or referral to other modes of therapy, such as surgery or chemotherapy.

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Countering the Environmental Implications of Radiation

The world was recently audience to a powerful and devastating nuclear disaster in Japan, leaving millions potentially at risk for the consequences of radiation exposure. To prepare for and combat these types of disasters, in 2005, the National Institute of Allergy and Infectious Diseases awarded the University of Pittsburgh School of Medicine one of only eight grants to create a Center for Medical Countermeasures Against Radiation. The grant was recently renewed for an additional five years.

The team is investigating the use of a mitochondria-targeted nitroxide (JP-4-039) to counteract the toxicity of radiation following a large scale exposure from a radiological or nuclear bomb. Working with a dermatologist, the team has designed a formulation so that the drug is applied topically like an ointment, cream, or skin patch.

SURGICAL ONCOLOGY

Case Study: Therapeutic Options for Managing Peritoneal Mesothelioma

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Haroon M. Choudry, MD

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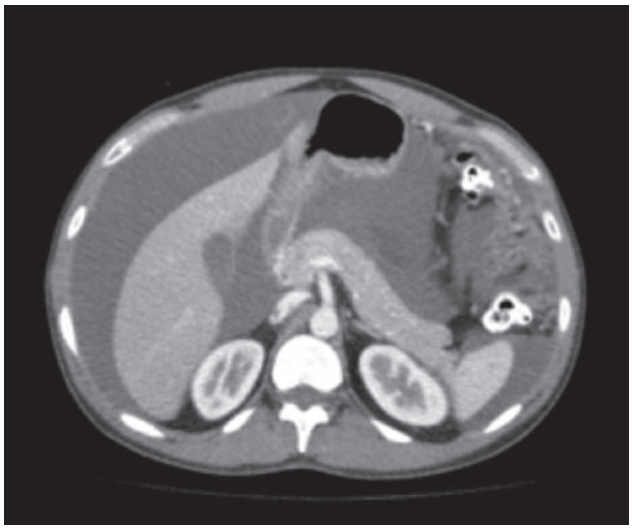
Patient Profile

- A 39-year-old male developed progressive abdominal discomfort, distention, fatigue, malaise, diarrhea, and experienced a 10-pound weight loss over a period of three months. A contrast-enhanced CT scan of the chest, abdomen, and pelvis revealed diffuse ascites, omental stranding, nodularity along the peritoneum, without evidence of abdominal parenchymal involvement or extra-abdominal metastasis (Figure 1). CEA and CA-125 tumor marker levels were normal.
- He underwent a diagnostic laparoscopy with omental/peritoneal biopsy and drainage of 3L of ascites at an outside institution. The surgeon described diffuse peritoneal carcinomatosis and subsequent pathology was consistent with epithelioid mesothelioma. He had no personal or family history of malignancies and no prior exposure to asbestos. He was referred to our institution and underwent cytoreductive surgery (radical tumor debulking with enbloc omentectomy, splenectomy, appendectomy, abdominal and pelvic peritonectomy, small bowel mesenteric stripping with argon beam-coagulation of nodules and wedge resection of an atypical lesion in segment III of the liver) in combination with hyperthermic intraperitoneal chemoperfusion (HIPEC) using Mitomycin C (40 mg for 100 minutes at 42°C). Complete cytoreduction was achieved, with isolated < 1mm nodules remaining on the small bowel (CC-1 resection) (Figure 2).
- Final pathology revealed malignant mesothelioma (epithelioid type) with local invasion into the appendiceal muscularis propria, however, the liver nodule was benign. Molecular studies revealed no EGFR-gene amplification (7p12) and no p16-gene (p21) deletion. His postoperative course was uneventful. Subsequent follow-up examinations and surveillance imaging at six-month intervals have revealed no evidence of disease recurrence (Figure 3). He is now 21 months post-resection.



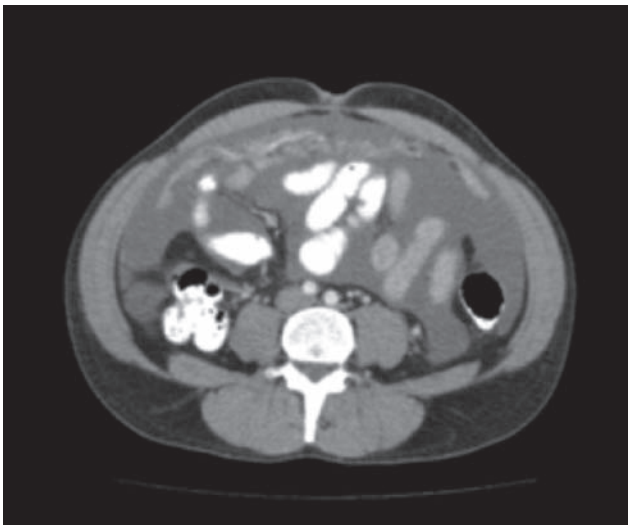


Figure 1: Representative pre-operative CT scan images demonstrating diffuse abdominal ascites, without parenchymal involvement or lymphadenopathy.

Discussion

Malignant mesothelioma (MM) is a rare, but aggressive, primary malignancy that most commonly develops from the serosal lining of the pleural or peritoneal cavities. Peritoneal mesothelioma (MPM) accounts for 10% to 20% of cases (250 to 500 cases per year).[1] Asbestos exposure is responsible for an estimated 80% of cases, although multiple secondary events, including genetic and environmental factors are required for malignant transformation, since only 5% of asbestos-exposed individuals develop MM.[2] Loss of $p16^{INK4a}$ gene product (CDKN2A-MTAP gene) is almost universal in MM and leads to inactivation of retinoblastoma (Rb) and p53 genes involved in cell cycle regulation. Krasinskas and colleagues demonstrated a strong correlation between p16 deletion and poor prognosis.[3] Other potential etiologic factors include Simian Virus 40 (SV40), a potent oncogenic virus that blocks tumor suppressor genes, ionizing radiation (thorotrast), chronic/recurrent peritonitis, and exposure to erionite.[2]

Clinical Presentation and Diagnosis

Patients most commonly present with abdominal discomfort and distention due to progressive accumulation of malignant ascites. Compressive symptoms lead to organ dysfunction, morbidity, and eventual mortality. MPM is an aggressive loco-regionally invasive disease that rarely involves lymph nodes (5% to 10%) or metastasizes extra-abdominally (3% to 5%). Classic CT scan findings include diffuse peritoneal dissemination without lymphadenopathy or extra-abdominal metastasis.[4] Serum CA-125, soluble mesothelin-related proteins (SMRP), and osteopontin are elevated in a subgroup of patients and may reflect burden of disease.[5-7]

Pathologists are frequently unable to differentiate between benign mesothelial proliferations, MPM, and adenocarcinomas based on routine staining, and often require a series of immunohistochemical markers. In general, positive calretinin and epithelial membrane antigen (EMA) staining with negative CEA staining is highly suggestive of MPM. MPM has a diverse spectrum of histopathologic patterns, as described by Battifora and McCaughey and categorized in the WHO classification (Table 1).[8]

The most consistent prognostic factors for improved survival include epithelial histology, negative lymph node disease, small nuclear size, complete cytoreduction (CC-0/CC-1) and M 5 mitoses/50 HPF.[9] A non-validated TNM-based clinico-pathologic staging system was proposed by the peritoneal surface oncology group in 2010 in which the peritoneal Cancer Index (PCI) was used as a surrogate for T-stage stratification.[10]

Therapeutic Modalities

The loco-regional nature of the disease lends itself to aggressive loco-regional therapies, including cytoreductive surgery (CRS) and perioperative intraperitoneal chemoperfusion (PIC). PIC refers to the application of heated chemotherapy directly into the peritoneal cavity during the surgical procedure (hyperthermic intraperitoneal chemoperfusion or HIPEC), or bathing the abdominal cavity with normothermic chemotherapy in the immediate postoperative period (early postoperative intraperitoneal chemotherapy or EPIC), or a combination. Cisplatin and doxorubicin are commonly used agents during PIC. Our recommended practice is to perform HIPEC using cisplatin alone, although others do advocate for the use of EPIC and/or doxorubicin. Surgical resection, based on Sugarbaker's specific peritonectomy procedures, eradicates macroscopic disease, while intraperitoneal chemotherapy targets microscopic disease. The rationale for hyperthermia includes direct toxic effects through impaired DNA repair, denaturing of proteins, induction of heat-shock proteins, induction of apoptosis, and inhibition of angiogenesis.[11] Currently, a combination of cisplatin and doxorubicin is considered the regimen of choice. There is no definitive evidence for any additional surgical complications related to hyperthermia, although there also are no randomized trials to show additional benefit of hyperthermic chemoperfusion over CRS alone.

Candidates for combined CRS and PIC must have an adequate performance status, be free of extra-abdominal metastatic disease, and have surgically resectable disease to M 2.5 mm (CC0/CC1). A systematic review of published peer-reviewed articles using combined CRS and PIC (HIPEC or combined HIPEC and EPIC) for MPM has been published. No randomized control trials, comparative studies, prior systematic reviews or meta-analyses were identified. The median survival range for the studies

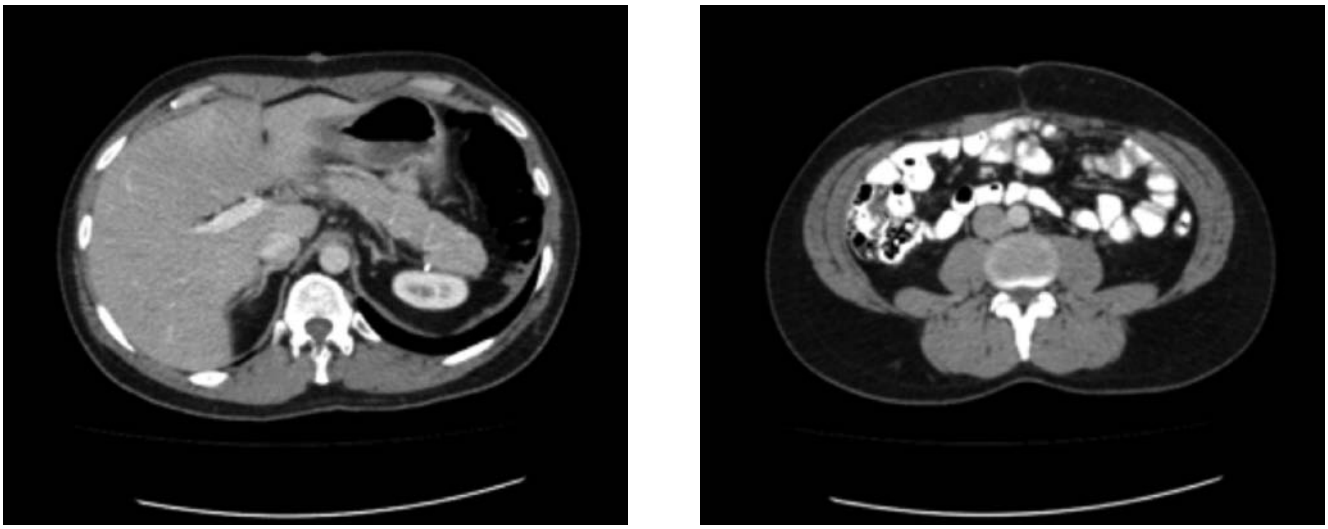


Figure 2: Representative three-month post-operative CT scan images demonstrating complete cytoreduction (CC-1) without evidence of disease.

was 34 to 92 months, with five- and seven-year survival rates of 29% to 59% and 33% to 39% respectively. The overall morbidity and mortality rates ranged from 25% to 40% and 0% to 8% respectively.[12]

Multimodality therapeutic strategies, including neoadjuvant or adjuvant chemotherapy protocols, are recommended for biologically aggressive variants of MPM (biphasic and sarcomatoid), given their poor prognosis, despite aggressive surgery. Most trials of systemic chemotherapy therapy have been performed in malignant pleural mesothelioma (MPlM). Cisplatin and doxorubicin regimens have demonstrated the highest response rates.[13] Recent randomized controlled trials using combination therapy of cisplatin with third generation antifolates, pemetrexed, and raltitrexed, have demonstrated response rates of 40%, mortality risk reduction of 10% at one year, and corresponding improvement in survival of six to eight weeks. This combination is currently considered the standard of care in patients with good performance status and unresectable disease and should be administered for a median of four to six cycles, unless progression or severe toxicity occurs.[14]

Molecular therapies targeting various pathways involved in tumor invasion and metastasis have been tested in preclinical, Phase I and Phase II studies. Proliferation, spread and invasion of MM cells is highly dependent on the aberrant activation of a number of growth factor receptors, including EGFR (ErbB1), PDGFR, VEGFR, HGFR, TGFβR, and IGFR. Molecular targeted therapies in various stages of research include EGFR-inhibitors (erlotinib), anti-VEGF humanized monoclonal antibody (bevacizumab), src-inhibitors (dasatinib), PI3K/AKT-inhibitors (perifosine), mTOR-inhibitors (rapamycin), proteosome-inhibitors (bortezumib), HDAC-inhibitors (vorinostat), and anti-mesothelin antibodies.[15]

Consensus Statement: Management Algorithm for MPM

A consensus statement was published in 2008 providing the following guidelines for the management of resectable and unresectable MPM.[16] Patients with resectable, low-malignant-potential mesothelioma (multicystic and papillary well-differentiated) should undergo complete CRS (CC-0/CC-1) and HIPEC. Patients with resectable mesothelioma of epithelial subtype should receive complete CRS, HIPEC, and EPIC with the consideration for adjuvant or neo-adjuvant systemic chemotherapy; whereas patients with biphasic and sarcomatoid subtypes should undergo complete CRS and HIPEC in combination with adjuvant or neo-adjuvant systemic chemotherapy. In the case of unresectable disease, maximal debulking procedure was recommended for low-malignant-potential mesothelioma (multicystic and papillary well-differentiated). Unresectable epithelial, biphasic, and sarcomatoid mesothelioma patients should undergo primary systemic chemotherapy with subsequent re-staging, followed by CRS and HIPEC in select cases with significant therapeutic response.[16]

Tumor Type	Histology	Incidence (%)	Biological Behavior
Malignant DMPM	Epithelial (Tubulopapillary, Solid non-glandular)	75%	Intermediate prognosis
	Sarcomatous	13%	Poor prognosis
	Biphasic (Mixed)	6%	Poor prognosis
	Undifferentiated	6%	Poor prognosis
Borderline/Low	Well-differentiated	Rare	Good prognosis
Malignant DMPM	Papillary		
	Multicystic	Rare	Good prognosis

Table 1: Malignant Peritoneal Mesothelioma: Pathologic Classification

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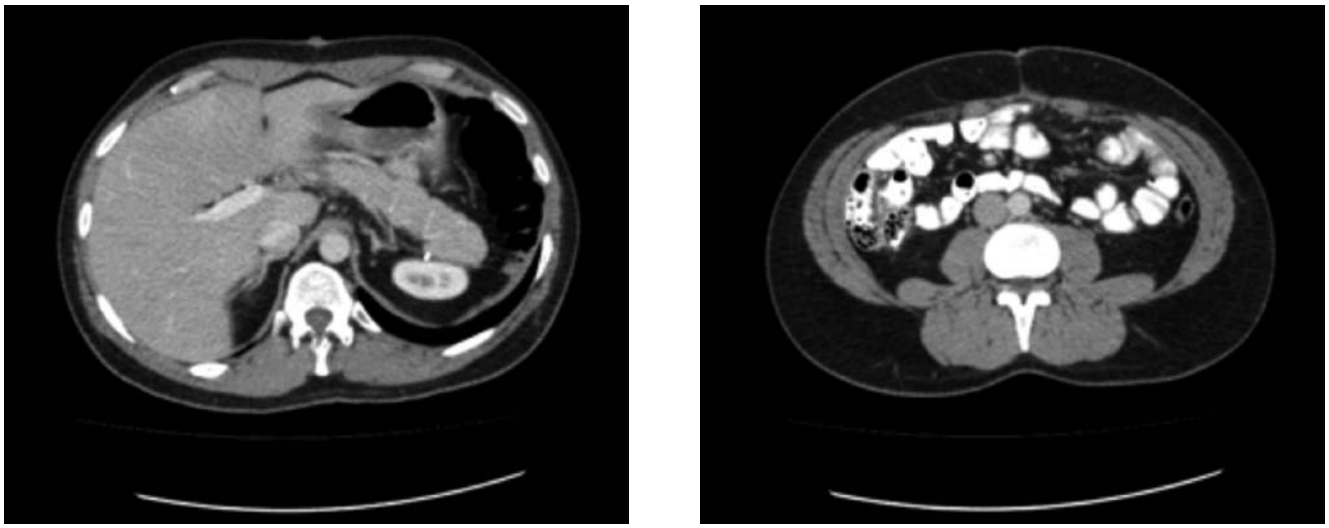

Figure 3: Representative 21-month postoperative CT scan images demonstrating no evidence of disease recurrence.

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UPMC CancerCenter launches Bladder Cancer Specialty Care Center

The American Cancer Society estimated that approximately 70,000 American men and women will be diagnosed with bladder cancer and almost 15,000 will die from it in 2011. Frequently, by the time blood is noticed in the urine and the diagnosis of bladder cancer is made, tumor cells have already invaded the muscular wall of the bladder and may be causing some obstruction of the kidneys. Current best practice recommendations for the treatment of muscle-invasive bladder cancer include initiation of neoadjuvant chemotherapy prior to surgical removal of the bladder whenever possible.

This coordinated effort requires good communication between a medical oncologist who will administer the chemotherapy and then, after a quick recuperation, a urologist, who will promptly proceed with removal of the bladder and complete the urinary reconstruction. Unfortunately, this decision process and implementation of therapy currently requires individual consultation visits and can result in some delay in initiation of therapy.

To help facilitate patient referrals, it is important to recommend a timely therapy plan and initiate therapy promptly. UPMC CancerCenter offers the Bladder Cancer Specialty Care Center, a multidisciplinary clinic for men and women recently diagnosed with muscle-invasive bladder cancer who should be considered for multimodality therapy. During a single clinic visit, both a medical oncologist and urologist will be available to provide simultaneous opinions and reach an individualized, consensus recommendation for the patient. The patient will then be able to take the multidisciplinary treatment recommendation back to the referring physician to institute therapy, or proceed with treatment through the UPMC CancerCenter network.

Expands availability of clinical trials

In addition to improving and expediting patient care, the Bladder Cancer Specialty Care Center will help to improve availability and increase participation in research studies and ongoing clinical trials for bladder cancer currently available at the University of Pittsburgh Cancer Institute (UPCI).

Research study investigates immune response mechanisms in bladder cancer tumors

Principal Investigators:

Jeff Gingrich, MD, Department of Urology

Pawel Kalinski, MD, PhD, University of Pittsburgh Department of Immunology

Superficial bladder cancer is commonly treated with instillations of bacillus Calmette-Guerin into the bladder. Although the mechanism of action is not completely understood, these instillations stimulate an intense immune response that reduces the incidence of tumor recurrence. This current research collaboration involves the characterization of chemokine expression in patient tumors and subsequent in vitro optimization of the response in these tumors. It is anticipated that this collaboration will lead to future human clinical trials testing the optimal strategies identified through these studies.

Bladder Cancer Support Group

In conjunction with the Shadyside Foundation, a UPCI bladder support group meets at Hillman Cancer Center the first Wednesday night of each month. The format is to provide informal interaction with urologists and medical oncologists involved in the management of bladder cancer, as well as other patients who may be at various stages of care for their bladder cancer.

For more information about the Bladder Cancer Specialty Care Center, current research studies and clinical trials, or the Bladder Cancer Support Group, please contact Dr. Gingrich at gingrichjr@upmc.edu or Dr. Kalinski at kalinskip@upmc.edu.

UPMC CancerCenter's Network of Care

The channels through which patients come to the community locations of UPMC CancerCenter for comprehensive cancer care may differ, but once a patient enters the system, they have access to an entire network of medical, radiation, and surgical oncologists, evidence-based treatment options, and the latest advances in cancer clinical care.

A Network of Physicians and Locations

At UPMC CancerCenter, we employ a hub-and-spoke model, anchored by our clinical and academic hub, Hillman Cancer Center, to offer cancer patients throughout western Pennsylvania and beyond convenient access to cancer care and innovative treatments close to home. This model of patient care provides easy access to care to an aging western Pennsylvania population and accommodates referrals between specialists at Hillman and our more than 30 satellite locations.

With more than 180 affiliated oncologists, this network represents a collection of some of the nation's most highly qualified and respected physicians and researchers in cancer medicine.

Clinical Pathways Program

Receiving cancer care in the community does not have to mean receiving anything less than the highest standards of care, thanks to the Clinical Pathways program. Developed by UPMC CancerCenter clinicians, Clinical Pathways provides uniform treatment plans for different types of cancer based on specific disease and patient parameters.

This standardization leads to better efficiencies, with fewer treatment errors, and improved patient satisfaction.

Pathways are constructed by disease-specific teams of physicians led by two co-chairs, a full-time academic faculty member with disease-site subspecialty expertise, and a community-based-practice physician.

The physicians review literature and clinical practices to determine the single best regimen for the specific disease, stage-by-stage, and its sub-categories. If more than one regimen fits the "best" category, then the regimen with the most favorable toxicity profile is chosen. As a top priority for each Pathway, whenever applicable, patients are recommended to participate in relevant clinical trials. Pathways use the Eastern Cooperative Oncology Group (ECOG) performance status to develop lines of treatment for common patient presentations. These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, evaluate how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

Access to Clinical Trials

Physicians understand that breakthroughs in research won't make a real impact until they reach the patient. At UPMC CancerCenter and the University of Pittsburgh Cancer Institute (UPCI), our physicians and researchers collaborate to rapidly translate basic science into effective new strategies for the prevention, detection, and treatment of cancer.

Strategies include the development of vaccines to block the progression of many cancers, the incorporation of new technologies that allow physicians to more precisely target treatment, as well as advances in minimally-invasive surgical procedures that are leading to reduced recovery times and better outcomes for patients.

Our research efforts have been recognized continuously by the National Cancer Institute, which has awarded UPCI the top distinction of Comprehensive Cancer Center since 1990, cementing our commitment to developing a comprehensive research infrastructure that ultimately supports superior cancer care.

As one of the nation's top centers for care and research, our nationally and internationally recognized specialists are changing the landscape of oncology.

UPMC PHYSICIAN RESOURCES

A Resource for You: UPMC Physician Resources brings world-class physicians and free educational opportunities to your computer. Learn new information while watching CME-accredited videos in the convenience of your home or office. Find out more at UPMCPhysicianResources.com/Cancer.

UPMC CancerCenter
Partner with University of Pittsburgh Cancer Institute

UPMC CancerCenter and University of Pittsburgh Cancer Institute

Nancy E. Davidson, MD
Director

UPMC has consistently received national recognition from *U.S. News & World Report* for offering one of America's top cancer programs. For more information about UPMC CancerCenter's clinical services, or University of Pittsburgh Cancer Institute research, call **1-800-533-UPMC** or visit **www.UPMCCancerCenter.com**.

For consults and referrals, call **412-647-2811.**

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

UPMC LIFE CHANGING MEDICINE

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