Heavily Treated mCRC.....what's next?
AIIMS Campus and Facilities
W-M-T

56 Yrs/Male Engineer presented in October 2010 with the chief complaint of
- Weight loss >13 kg X 7 month
- Bleeding per rectum X 2 months
- Passage of blood clots during defecation X 2 month
PAST MEDICAL HISTORY:

- Hypertension X 8 years controlled on medication
- Diabetes Mellitus X 5 years controlled on OHA
PERSONAL HISTORY:
- Occasional alcohol intake
- Non smoker
- Non vegetarian

FAMILY HISTORY:
4 brothers, all Diabetic
No history of malignancy
BASELINE EXAMINATION

- ECOG-1

O/E: 5X6 cm tender palpable lump right flank

P/R Finding:

- Proliferating mass ano-rectal region lower margin 3cm above anal verge
BASELINE INVESTIGATIONS
CECT:
- Hypo dense liver lesion segment VII/VIII 4.3X4.5 cm
- Circumferential wall thickening in the region of the ano-rectum
- Multiple enlarged lymph nodes noted in the peri rectal region
PET-CT:
- Ill defined asymmetrical nodular FDG at the ano-rectal junction
- Multiple enlarged peri rectal lymph node noted
- Metastatic lesion in segment VII/VIII of the liver
LOWER GI ENDOSCOPY:
○ ulcerated polypoidal friable growth in ano rectum starting just above anal verge

HISTOPATHOLOGY:
○ Moderately differentiated adenocarcinoma rectum

CEA:
○ 43 ng/ml

KRAS:
○ Wild type (Codon 12,13,61)

STAGE: T3N1M1
TREATMENT AND RESPONSE

12 Cycles FOLFOX+Cetuximab
(Dec 2010- June 2011)

PET-PR

Underwent APR with permanent colostomy,Liver metastasis was not amenable to surgical resection or RFA (October 2011)

Post APR 3 Cycle of FOLFIRI+Cetuximab
(Dec2011-Jan 2012)
SBRT 45Gy/25# Liver lesion as SOLs was not amenable to resection due to involvement of IVC and Hepatic vein (Feb 2012-March 2012)-PET-PR (Apr 2012)
Alcohol Injection SOLs  
October 2012

TACE(Mitomycin-C+Irinotican)  
Nov 2012

Progressed in July 2013

FOLFIRI+Cetuximab (August 2013-May 2014)-SD

Maintenance Cetuximab- Progressive Disease on PET CT in Dec 2014
PET-CT April 2015

FOLFOX+Bvecizumab

December 2014-April 2015

Post C6 PET-CR

All India Institute of Medical Sciences, New Delhi, India.

W18F-FDG WHOLE BODY PET-CT STUDY

Patient Name Waman

Age/Sex: 56/M

Study ID: FDG/427320/15

Date: 06/04/2015

Indication: Ca rectum, post surgery, chemotherapy and RT

Procedure: PET-CT acquisition was done 45 to 60 minutes after injection of 10 mCi (adult)/0.2 mCi/kg (children) 18F-FDG by intravenous route, from the level of orbits to mid-thigh. CT was done for attenuation correction and anatomical localization. Additional spot views were taken if indicated.

PET-CT Findings:

Head and Neck: Normal physiologic FDG distribution is seen in the head and neck region. Visualized paranasal sinuses, skull base, pharynx, larynx and thyroid do not show any abnormality on CT. No lymphadenopathy noted.

Thorax: Multiple soft tissue nodules of variable sizes with cavitation are noted in bilateral lungs with no significant FDG uptake. Subcentimetric peribronchial, subcarinal, AP window lymph nodes are seen with calcification. Physiologic FDG uptake is seen in the myocardium. Large airways, pleura heart, great vessels and other mediastinal structures appear normal on CT.

Abdomen-Pelvis: Liver shows multiple hypodense lesions in both lobes of liver with no significant FDG uptake. (largest measures 6.2 x 5.8cm, in segment VIII/II/V). Hernia noted on left lateral abdominal wall with bowel loops as its contents. Left renal exophytic cyst noted. Normal FDG distribution is noted in the spleen, right kidney and urinary bladder. Gall bladder, spleen, right kidney, stomach, adrenals, pancreas and urinary bladder appears normal on CT. No ascites is noted.

Skeletal System: Physiologic FDG distribution is seen in the entire axial and appendicular skeleton.

Impression:

- Metastatic disease involving bilateral lungs, liver with no significant tracer uptake.
- Compared to previous PET-CT (FDGN/6026/14, dated 8/12/2014), there is resolution uptake of lung and liver lesions and lymph nodes suggestive of complete metabolic response.

Prof Rakesh Kumar
Capecitabine+Avastin maintenance – Progressive Disease on PET CT in October 2015

FOLFIRI+Avastin-(October 2015-May 2016)-PD
**RECENT PET CT (May 16)**

- FDG avid multiple pulmonary lesions of varying size in both lungs
- FDG avid multiple irregular hypodense lesions are noted in seg IV/VIII
- FDG avid enlarged periportal and precaval lymphnode - PROGRESSIVE DISEASE
CURRENT STATUS

- ECOG-1
- On Regorafenib 160 mg D21/28 (Aug 2016……Current

CURRENT TOXICITY

- Grade-II HFS
- Grade-II diarrhea
- Grade-I Asthenia
- Grade-I Vomiting
- Grade-II mucositis
- CBS, LFT, KFT-WNL
TREATMENT OPTIONS

Money Vs Effectiveness
Trifluridine/Tipiracil (TAS-102):

- **RE COURSE: TAS-102** Approved in 2015 as single agent in refractory CRC
- In Phase III RE COURSE Study demonstrated OS benefit from 5.3 months 7.1 months over placebo
- High Grade 3 AE’s (98% vs 52%), all of which are manageable
- Trifluridine/Tipiracil has shown synergy with oxaliplatin, bevacizumab, or an EGFR inhibitors
- In phase I/II study Trifluridine/Tipiracil has shown PFS of 16 weeks
WHICH ONE TO BE USED FIRST Regorafinib OR Trifluridine/Tipiracil???

<table>
<thead>
<tr>
<th>TABLE 1. Current Standard of Care in Refractory Colorectal Cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>Population and Type of Study</strong></td>
</tr>
<tr>
<td>N = 760, 2:1 ratio (505 vs 255), refractory mCRC</td>
</tr>
<tr>
<td>(2 lines of prior treatments)</td>
</tr>
<tr>
<td>CORRECT: RCT</td>
</tr>
<tr>
<td>N = 800, 2:1 ratio (534 vs 266), refractory mCRC</td>
</tr>
<tr>
<td>(2 lines of prior treatments)</td>
</tr>
<tr>
<td>RECOUERSE: RCT</td>
</tr>
</tbody>
</table>

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; RCT, randomized controlled trial.
Ramucirumab:

- Phase III RAISE Trial
- N=1072
- FOLFIRI plus ramucirumab (n = 536) or FOLFIRI plus placebo (n = 536) given in 2-week cycles
- Median overall survival was 13.3 months in the ramucirumab group vs 11.7 months
- Progression-free survival was also significantly prolonged in the ramucirumab group (median, 5.7 vs 4.5 months)
- The most common events leading to discontinuation of ramucirumab were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- The most common serious adverse events in the ramucirumab group were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
BRAF INHIBITORS;

- First round of screening for mutations in KRAS oncogene codons 12, 13 and 61 is already negative.
- Any role of repeat KRAS to look for mutations in KRAS exon 4 and in NRAS exons 2, 3 and 4, BRAF.
- BRAF inhibitors alone has shown minimum activity in mCRC.
- Vemurafenib (BRAF inhibitor) combined with panitumumab (EGFR inhibitor), the ORR of 12%.
- Combination of BRAF and MEK inhibitors produced an ORR of 10%.

**TABLE 3. Promising Combination Treatments in BRAF Mutated Colorectal Cancer**

<table>
<thead>
<tr>
<th>Population and Type of Study</th>
<th>Setting/Premise</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>N = 15, refractory mCRC</td>
<td>Vemurafenib + panitumumab</td>
<td>ORR: 12%</td>
<td>Yaegeret et al., 2015</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
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<tr>
<td>N = 20 vs 26, refractory mCRC</td>
<td>Dabrafenib + trametinibvs</td>
<td>ORR: 10% vs 26%</td>
<td>Atreya et al., 2015</td>
</tr>
<tr>
<td></td>
<td>Dabrafenib + trametinib + panitumumab</td>
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<tr>
<td>Phase I</td>
<td></td>
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<tr>
<td>N = 19, refractory mCRC</td>
<td>Vemurafenib + cetuximab + irinotecan</td>
<td>ORR: 35%, PFS: 7.7 months</td>
<td>Hong et al., 2015</td>
</tr>
</tbody>
</table>

mCRC, metastatic colorectal cancer; ORR, overall response rate; PFS, progression-free survival.
MSS (role of immunotherapy in MSS mCRC [95% in stage IV mCRC]

- As of now Immunotherapy has shown activity in MSI-High mCRC i.e 5% patients of mCRC
- MSS-CRC (which are about 95% of Stage IV cases) has proven much more resistant to immunotherapy treatments than the comparatively rare MSI-high form of CRC
- So what about these 95% patients
- Abstract 3502 “Clinical activity and safety of Cobimetinib (anti PD-1) and Atezolizumab(MEK inhibitor) in colorectal cancer (CRC)” ASCO Annual Meeting 2016

- Small study N 23
- The 6-month overall survival rate (OS) rate was 72%. Partial response (PR) confirmed per RECIST v1.1 was achieved by 4 patients, and 5 patients showed stable disease
- Reasoning that MEK inhibition leads to an upregulation of major histocompatibility complex class I (MHC I) expression on tumor cells and increased intratumoral T-cell infiltration
- Cobimetinib could enhance the anti-PD-L1 activity of atezolizumab in patients with MSS mCRC and advanced solid tumors.
- Larger trials are need for definitive answer
FISH of Her2Neu

- HER2 is amplified in 5% of WT exon 2 KRAS mCRC patients.
- The HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with standard therapies, including EGFR-targeted agents, indicating that the dual anti HER2 therapy is effective and deserves further clinical assessment in earlier lines of treatment of HER2+ mCRC patients.

*HERACLES Trial, Abstract no: 3508, ASCO Annual meeting 2016

T-DM1: HER2 amplification as a ‘molecular bait’ for trastuzumab-emtansine (T-DM1) precision chemotherapy to overcome anti-HER2 resistance in HER2 positive metastatic colorectal cancer:

*The HERACLES-RESCUE trial. TPS 774, ASCO Annual meeting 2016*
STEM CELL INHIBITORS: BBI 503

- NANOG expression, a biomarker that promotes proliferation, migration, and poor prognosis in colorectal cancer
- BBI 503 has shown a disease control rate of 56% compared with 13% in patients without NANOG expression
- This Phase I study suggests that stem cell inhibitors could potentially overcome poor prognosis factors such as NANOG
**TABLE 4. Agents That May Resensitize RAS Wild-Type Tumors to EGFR Inhibition in Colorectal Cancer**

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<tbody>
<tr>
<td>N = 16, refractory mCRC (cetuximab treated)</td>
<td>AUY 922 (HSP 90 inhibitor) + cetuximab</td>
<td>OS: 37.7 weeks</td>
<td>Subramaniam et al, 2015&lt;sup&gt;23&lt;/sup&gt;</td>
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<tr>
<td>Phase I</td>
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<tr>
<td>N = 9 (panitumumab treated) vs 15 (panitumumab naïve), refractory mCRC</td>
<td>BBI 608 (stem cell inhibitor) + panitumumab</td>
<td>PFS: 16.4 vs 9 weeks</td>
<td>Hubbard et al, 2015&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
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</tbody>
</table>

mCRC, metastatic colorectal cancer; Hsp 90, heat shock protein 90; OS, overall survival; PFS, progression-free survival
Thank you very much for your time and patience
DISCUSSION...