5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Capecitabine–Based Chemoradiation Therapy in the Preoperative Treatment of Rectal Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVES

- Apply the results of new research when recommending neoadjuvant chemoradiation therapy to patients with locally advanced rectal cancer.
- Recognize the effect of capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

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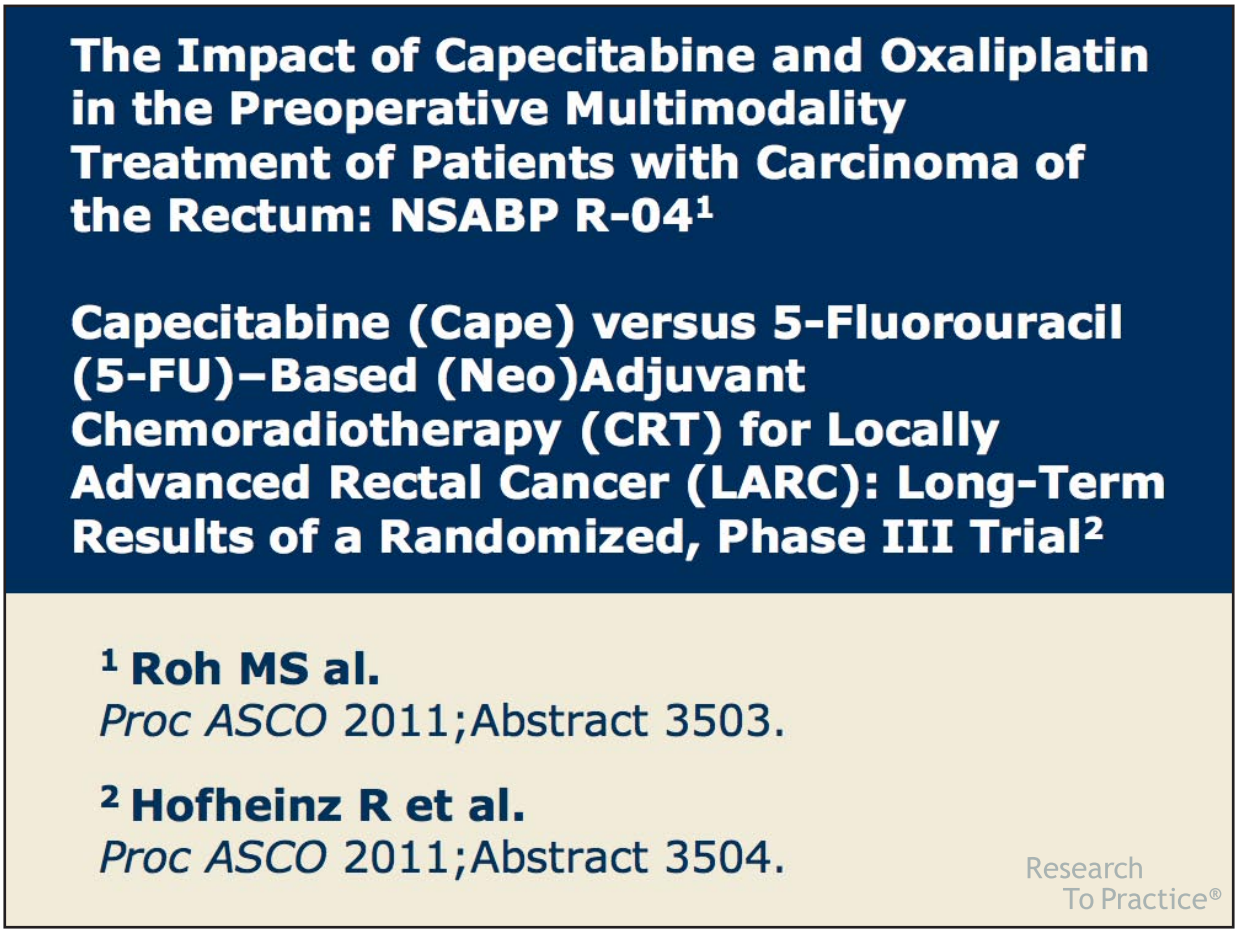
Capecitabine–Based Chemoradiation Therapy in the Preoperative Treatment of Rectal Cancer

Presentations discussed in this issue

Roh MS et al. **The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04.** *Proc ASCO* 2011;**Abstract 3503**.

Hofheinz R et al. **Capecitabine (cape) versus 5-fluorouracil (5-FU)-based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, Phase III trial.** *Proc ASCO* 2011;**Abstract 3504**.

Slides from presentations at ASCO 2011 and comments from Charles D Blanke, MD and Steven R Alberts, MD



The Impact of Capecitabine and Oxaliplatin in the Preoperative Multimodality Treatment of Patients with Carcinoma of the Rectum: NSABP R-04

Roh MS et al.
Proc ASCO 2011;Abstract 3503.

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NSABP R-04: Outcomes by Treatment

5-FU versus Capecitabine (Cape)			
	5-FU (± Oxaliplatin)	Capecitabine (± Oxaliplatin)	*p*-value
pCR rate, (n=719, 707)	18.8%	22.2%	0.12
SSS, (n=727, 710)	61.2%	62.7%	0.59
SD, (n=188, 187)	20.7%	23.0%	0.62

Oxaliplatin (Ox) versus None			
	(5-FU or Capecitabine) Oxaliplatin	(5-FU or Capecitabine) No Oxaliplatin	*p*-value
pCR rate, (n=578, 580)	20.9%	19.1%	0.46
SSS, (n=584, 582)	60.4%	63.6%	0.28
SD, (n=151, 152)	19.2%	23.0%	0.48

pCR, pathologic complete response; SSS, sphincter-saving surgery; SD, surgical downstaging

Roh MS et al. *Proc ASCO* 2011;Abstract 3503.

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NSABP R-04: Select Toxicities

GI Toxicity	(5-FU or Cape) Oxaliplatin n = 631	(5-FU or Cape) No Oxaliplatin n = 622	*p*-value
Diarrhea (Grade 3/4)	15.4%	6.6%	<0.0001
	5-FU (± Ox) n = 625	**Cape (± Ox) n = 628**	***p*-value**
Diarrhea (Grade 3/4)	11.2%	10.8%	0.86

Surgical Complications	5-FU	5-FU + Ox	Cape	Cape + Ox
Any complication	34.9%	37.0%	36.9%	40.2%

Roh MS et al. *Proc ASCO* 2011;Abstract 3503.

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Author Conclusions

- Administration of capecitabine with preoperative radiation therapy achieved rates similar to continuous IV infusion 5-FU for:
  - Surgical downstaging
  - Sphincter-saving surgery
  - Pathologic complete response
- Addition of oxaliplatin did not improve outcomes and added significant toxicity.
- Longer follow-up will be needed to assess local-regional tumor relapse, disease-free survival and overall survival.

Roh MS et al. *Proc ASCO* 2011;Abstract 3503.

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Capecitabine (Cape) versus 5-Fluorouracil (5-FU)–Based (Neo)Adjuvant Chemoradiotherapy (CRT) for Locally Advanced Rectal Cancer (LARC): Long-Term Results of a Randomized, Phase III Trial

Hofheinz R et al.
Proc ASCO 2011;Abstract 3504.

Efficacy Endpoints

Median Follow-Up: 52 Months	Capecitabine (n = 197)	5-FU (n = 195)	*p*-value
5-year overall survival (OS)	75.7%	66.6%	0.052[1]
3-year disease-free survival (DFS)	75.2%	66.6%	0.035
5-year DFS	67.8%	54.1%	

Comparison of Hand-Foot Skin Reaction (HFS) and Survival			
	Capecitabine HFS - Any Grade (n = 62)	Capecitabine No HFS (n = 135)	5-FU All Patients (n = 195)
5-year OS	91.4%[2]	68.0%	66.6%
3-year DFS	83.2%[3]	71.4%	66.6%

[1] Test for noninferiority at 5 years: $p < 0.001$; Exploratory test for superiority at 5 years: $p = 0.053$; [2] Test for superiority: $p = 0.001$ vs Cape no HFS (n = 135) and $p < 0.0001$ vs remaining population (n = 330); [3] Test for superiority: $p = 0.031$ versus Cape no HFS (n = 135) and $p = 0.004$ versus remaining population (n = 330)

Hofheinz R et al. *Proc ASCO* 2011;Abstract 3504.

Neoadjuvant Stratum: Trend toward Improved Downstaging with Capecitabine

	Comparison (χ^2 test)	
	Clinical Staging	Pathohistology
T status	$p = 0.5$	$p = 0.07$
N status	$p = 0.7$	$p = 0.09$

- **Patients receiving capecitabine exhibited:**
  - Less ypN-positive tumors ($p = 0.09$)
  - Improved T downstaging (ie, ypT0 – 2) ($p = 0.07$)
  - More pCR (ypT0 ypN0): 13.2% vs 5.4% ($p = 0.16$)

Hofheinz R et al. *Proc ASCO* 2011;Abstract 3504.

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Author Conclusions

- Both treatment regimens were relatively well tolerated (data not shown).
- Patients receiving Cape had more HFS, proctitus, diarrhea and fatigue, while alopecia and leukopenia were more often observed with 5-FU (data not shown).
- In the neoadjuvant Cape stratum, a trend toward improved downstaging and a higher rate of pCR was observed.
- 3-year DFS was significantly better with Cape.
- 5-year survival rate with Cape was noninferior to 5-FU.
  - Exploratory test for superiority was borderline significant.
- Capecitabine may replace 5-FU in the perioperative treatment of locally advanced rectal cancer.

Hofheinz R et al. *Proc ASCO* 2011;Abstract 3504.

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Investigator Commentary: Results from the NSABP-R-04 and German MARGIT Study Group Trials

At ASCO 2011, the NSABP-R-04 cooperative group trial for patients with rectal cancer reported no real benefit from oxaliplatin on surgical outcomes. I wouldn't use oxaliplatin during radiation therapy myself until we have more data. The NSABP-R-04 study did suggest, however, that capecitabine is as good as IV fluoropyrimidines, so that was important.

Charles D Blanke, MD

I believe the biggest pieces of new information that came out of this year's ASCO meeting were the early reports from trials evaluating either capecitabine or 5-FU with or without oxaliplatin and radiation therapy for patients with rectal cancer. As has been reported in some previous data sets, the use of oxaliplatin does not seem to enhance the response rates or resection rates in patients with rectal cancer.

A data set on the use of capecitabine versus 5-FU-based neoadjuvant therapy for patients with locally advanced rectal cancer was also reported. Those data suggest that capecitabine is a reasonable alternative to 5-FU. It's certainly much easier for most patients to take a pill rather than have an IV infusion for 5 to 6 weeks. The biggest point most people have to be aware of would be related to the toxicity with the continuous use of capecitabine for 5 to 6 weeks.

Steven R Alberts, MD

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