5 Minute JournalClub

Key ASCO Presentations
Issue 8, 2010

Use of Bevacizumab in the Neoadjuvant Setting for Patients with Locally Advanced 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 serial 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 patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Describe the results of a feasibility study examining neoadjuvant FOLFOX with bevacizumab and without pelvic radiation therapy for patients with locally advanced rectal cancer.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: Bristol-Myers Squibb Company, ImClone Systems Incorporated; Paid Research: Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals Inc.

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To go directly to the slides and commentary, **click here**.

Medical oncology has always challenged both patient and physician to make brutally difficult decisions concerning treatments that often provide modest benefits at the expense of significant toxicity. Nowhere has this paradigm been more evident than at the recent GI session in Chicago where French investigators **reported** that in advanced pancreatic cancer FOLFIRINOX (with full-dose oxaliplatin and irinotecan) not only improved progression-free survival and response rate but also overall survival (from 6.8 to 11.1 months). Within a couple of weeks of the presentation, I had chatted with Rich Goldberg, Axel Grothey and Malcolm Moore about this controversial data set. The bottom line? In spite of increased myelosuppression, particularly neutropenia, and other predictable problems with the combination, all three investigators are now considering FOLFIRINOX for younger, healthier patients.

Another provocative **data set** out of ASCO was a Spanish trial demonstrating that in patients receiving XELOX/bevacizumab as first-line therapy for metastatic colon cancer, maintenance therapy with bev alone may be as effective as maintenance with XELOX/bev. Axel, who was still a bit cranky after watching Spain run circles around his German team in the World Cup, believes this study has an inferior design to the ongoing German trial comparing capecitabine/bev to bev as maintenance that also includes a control arm of no maintenance.

The latest in a series of innovative pilot studies from Memorial examining local therapy in colon and rectal cancer also generated some buzz in Chicago. Deborah Schrag **reported** on 30 patients with T2-3 primary rectal cancer, many with nodal mets, who received pre-op FOLFOX/bev *without* radiation therapy. The resectability rate in this experience was similar to those that have been seen with neoadjuvant chemo/radiation therapy. Although this strategy is far from ready for prime time, Axel told me about a patient he had recently treated with this approach because prior radiation therapy for cervical cancer precluded further RT. Perhaps not surprisingly, she responded to FOLFOX and then underwent successful surgery.

Several other notable ASCO papers focused on EGFR antibody treatment for colorectal cancer, specifically cetuximab. K-ras status (wild type) was once again determined to have predictive value in the metastatic setting while B-raf was not, and data from an **NCCTG trial** evaluating mFOLFOX6 alone or with cetuximab in the adjuvant setting

disappointingly demonstrated no additional benefit with the combination, regardless of K-ras status.

The concluding sound bite from this, our final ASCO highlights issue, is another chemo/bev study that resulted in a response and a progression-free survival advantage but no survival benefit. "**AVAGAST**" focused on gastric cancer, and because survival was the primary endpoint, the study was considered negative. At the prostate cancer session, similar results and conclusions were reported for docetaxel/bevacizumab, and the recent ODAC opinion on chemo/bev in breast cancer suggests that the acceptability bar is being raised, even for an agent whose most significant toxicity is often financial.

Enjoy the rest of your summer. We will be back right around Labor Day with our next installment of Consensus or Controversy — this time in non-small cell lung cancer.

Neil Love, MD
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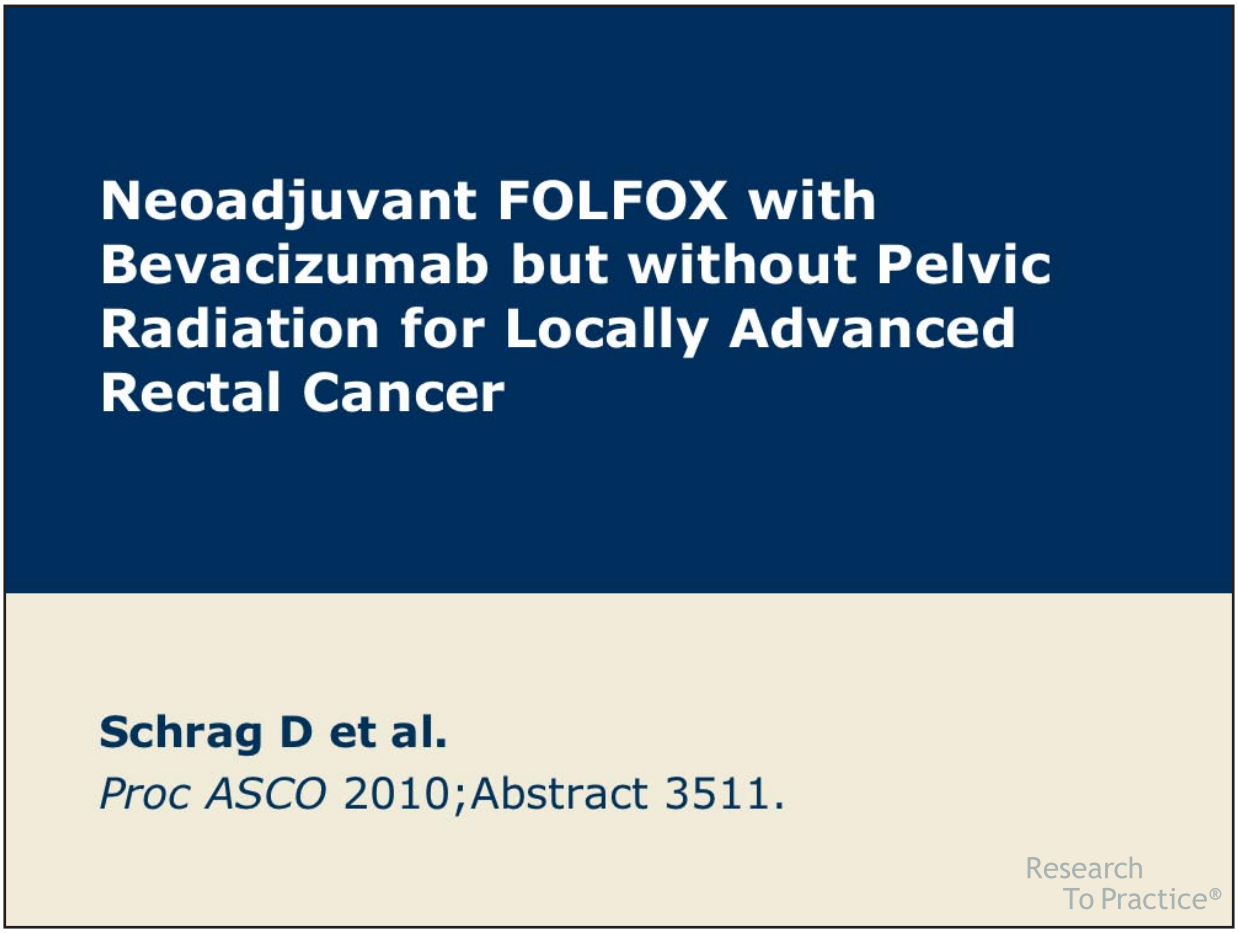
Use of Bevacizumab in the Neoadjuvant Setting for Patients with Locally Advanced Rectal Cancer

Presentation discussed in this issue

Schrag D et al. **Neoadjuvant FOLFOX with bevacizumab but without pelvic radiation for locally advanced rectal cancer.** *Proc ASCO* 2010;**Abstract 3511**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Axel Grothey, MD (7/9/10) and Alan P Venook, MD (6/16/10)



Introduction

- Standard therapy for locally advanced rectal cancer is 5-FU-based chemotherapy combined with radiation therapy and followed by surgery and adjuvant chemotherapy.
- Although pelvic XRT nearly eliminates the risk of local recurrence (LR), it can be associated with long-term adverse effects on bowel, bladder and sexual functions and can induce myelosuppression.
- Improvements in systemic chemotherapy for patients with Stage III colon cancer and in surgical techniques for patients with rectal cancer have improved patient outcomes.
- **Current study objective:**
  - Assess the feasibility of achieving R0 resection with neoadjuvant FOLFOX plus bevacizumab administered without pelvic XRT in patients with newly diagnosed, locally advanced rectal cancer.

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

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Pilot Study Design

Accrual: 32

Eligibility (N = 30)

Newly diagnosed clinical stage II or III rectal adenocarinoma

uT2N1-2 or uT3N0-2 primary rectal tumor

Candidate for lower anterior resection, FOLFOX and bevacizumab (Bev)

→ **FOLFOX + Bev**
FOLFOX + Bev x 4 → FOLFOX x 2

→ Patients with progressive or stable disease → XRT + 5-FU

→ Patients with clinical regression → Surgery*

*Post-operative treatment at discretion of physician. FOLFOX x 6 recommended; no post-operative Bev provided.

XRT = radiation therapy

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

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Results (Mean Follow-Up 18.2 Months)

Event Rate	N	%
R0 resection — all pts	32/32	100
R0 resection, on study	30/30	100
Pts needing pre-op pelvic XRT	0/30	0
Pathologic complete response	8/30	27
Deaths	1/30	3
LR rate	0/30	0
Distant recurrence — all lung	3/30	10

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

Conclusions

- Neoadjuvant FOLFOX-based chemotherapy without XRT does not appear to compromise the R0 resection rate in patients with locally advanced rectal cancer not requiring abdominoperineal resection.
  - R0 resection rate, all patients accrued (n = 32): 100%
  - R0 resection rate, patients on study (n = 30): 100%
- The pathologic complete response (CR) rate was 27% (8/30 patients).
- These data suggest that appropriately selected patients with locally advanced rectal cancer may forego pelvic XRT without adversely affecting R0 resection and pathologic CR rates.
- Based on these preliminary results, a cooperative group study is planned to examine neoadjuvant FOLFOX without XRT in patients with locally advanced rectal cancer.

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

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Investigator comment on the results of a study of neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

The standard treatment approach for most patients with locally advanced rectal cancer is neoadjuvant chemoradiation therapy. Most acknowledge that radiation therapy is probably the more toxic component of this treatment, particularly the long-term side effects. I have patients who have radiation proctitis, which is nasty and leads to pain, constant diarrhea and sphincter dysfunction. It would be a paradigm shift if we could utilize highly active systemic therapy without radiation therapy.

Memorial Sloan-Kettering Cancer Center had two interesting pilot studies — one with FOLFOX with bevacizumab and one with FOLFOX alone — and in their series, they had an approximately 30 percent pathologic complete response rate for patients with mid- or higher-rectum adenocarcinomas without radiation therapy, which is as good as it gets when you talk about 5-FU-based neoadjuvant chemoradiation therapy. The critical issue this raises in rectal cancer is the importance of adequate imaging. It is imperative to identify patients who are good candidates — those with T3N0, and perhaps T3N1 disease, but definitely not more than that.

Both ACOSOG and CALGB have proposals in their portfolio right now to test this strategy prospectively in a multicenter setting.

Interview with Axel Grothey, MD, July 9, 2010

Investigator comment on the results of a study of neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

This study is a potential game changer. The Memorial Sloan-Kettering Group speculated that there were some patients who were currently receiving chemoradiation therapy for rectal cancer who didn't need it. We all agree on that concept, but the challenge is in figuring out which patients don't need radiation therapy to avoid putting them at risk.

The Memorial group treated about 30 patients, and they were aggressive in monitoring them. They did baseline CT scans and pelvic scans and did MRI in the interim to make sure patients had responding disease. If the patients' disease was responding, they were treated essentially with four courses of chemotherapy. The patients went to surgery, and if they had an R0 or a resection of all known disease, that was it. They didn't receive radiation therapy. By all accounts this was a positive study, which suggests that radiation therapy is not necessary for every patient. This is huge because it spares patients a lot of toxicity, but physicians should not take it as a carte blanche to practice this outside of clinical trials, which are currently planned in the cooperative group setting.

Interview with Alan P Venook, MD, June 16, 2010

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