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Preoperative Radiation Therapy in Combination with Weekly Paclitaxel and Oral Glutamine for Rectal Cancer

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Abstract -
Optimal treatment for clinically localized rectal cancer continues to evolve. Preoperative chemoradiotherapy (CRT) may diminish radiation (XRT) toxicity and preserve the anal sphincter. In this prospective, phase 2, single institution trial, we studied preoperative neoadjuvant weekly paclitaxel (P), concurrent XRT, and oral glutamine in patients with rectal cancer and either transmural or nodal (N+) disease. Patients received intravenous weekly P concurrent with XRT and oral glutamine. Patients were restaged 4 weeks following the end of CRT, and then underwent resection. Patients were then offered 4 months of postoperative 5-fluorouracil (5-FU)-based adjuvant chemotherapy.

Twenty-five of 25 planned patients were enrolled. The median age was 58 years (range 40-83). At initial enrollment:
- there were 15 distal and 9 mid-upper primary rectal tumors
- initial clinical stage: T2 5%, T3 90%, T4 5%; N- 59%, N+ 41%
- all were M0

Ninety-six percent of planned doses of paclitaxel were administered and 96% of patients received the full dose of XRT.

GI/local toxicity was graded per SWOG criteria. Most severe toxicity during preoperative chemoradiotherapy included grade 3 anemia and grade 3 neutropenia; grade 3 and grade 4 diarrhea; grade 2 dysuria and grade 4 perianal desquamation.

Ninety-two percent of patients were surgically resected. Low anterior resection (LAR) was accomplished in 77% and 23% patients required abdominoperineal resection (APR).
- final pathologic stage: Tis/T1 18%, T2 23%, T3 59%; N- 68%, N+ 32%
- there was 13% progression to metastatic disease prior to surgery

Eighty-three percent of patients received postoperative 5-FU-based chemotherapy. Fourteen (64%) of patients remained disease-free after surgery and completion of adjuvant chemotherapy; 12 are still living. Five year disease-free survival is 64% and 5 yr overall survival is 76%. We conclude that this therapy is a tolerable alternative to current standard neoadjuvant regimens, does not lead to an increase in postoperative
complications and demonstrates down staging of primary rectal tumors allowing preservation of anal sphincter function.

Introduction -
Nearly 42,000 patients are diagnosed with rectal cancer each year. There has been constant evolution regarding optimal treatment for clinically localized rectal cancer. The current standard of care for the majority of T2-T4 tumors is preoperative neoadjuvant chemoradiotherapy followed by potentially curative surgery. The main goals of treatment aside from cure are to minimize toxicity and optimize patients’ quality of life during and after treatment. Definitive management of low-lying rectal cancers has a greater likelihood of impacting patients’ quality of life. Continued research to optimize treatment options will most benefit this population of patients with regard to quality of life after surgery. The leading concept behind preoperative neoadjuvant therapy is reduction in tumor burden and down staging. The goal is to minimize the resection field, preserve satisfactory sphincter function and leave as few patients as possible with permanent colostomies. Current standard of care also includes post operative 5-fluorouracil (5-FU)-based adjuvant chemotherapy. Paclitaxel, an antineoplastic agent, has been widely used as a solitary agent or in combination with other chemotherapeutic agents and radiation therapy against a number of neoplastic diseases including breast, pancreatic, lung, ovarian, and gastric cancers. No studies have examined the role of this agent against rectal cancer.

Paclitaxel is an attractive agent in preoperative chemoradiation given its role as a radiation sensitizer. Paclitaxel blocks cells in the G2/M phase of the cycle by blocking mitotic spindle function and holding cells in a state known to be up to 4-fold more sensitive to radiation than other cell cycle phases. Thus, the ability of paclitaxel to block cells in the G2/M phase of the cell cycle appears to directly cause its radiation sensitizing ability. Recent research has also provided insight to the role of paclitaxel as a mediator of reactive oxygen species and subsequent damage to bystander cancer cells. In either case, paclitaxel is an appropriate choice for preoperative chemotherapy with concurrent radiation therapy. While the current trend is towards oral chemotherapeutics to optimize patient quality of life, we believe paclitaxel may be a highly useful alternative in patients who cannot tolerate the current standard of care or these newer oral therapies. Therefore we studied preoperative neoadjuvant weekly paclitaxel, concurrent radiation (XRT), and oral glutamine in patients with rectal cancer and either transmural or nodal (N+) disease as suggested by rectal exam, pelvic MRI, CT scan, or transrectal ultrasound.

Methods -
Twenty-five patients were enrolled in a prospective, phase 2, single institution trial evaluating the role of preoperative paclitaxel and radiation in rectal cancer. Patients with rectal cancer and either transmural or nodal (N+) disease as suggested by rectal exam, pelvic MRI, CT scan, or transrectal ultrasound were consented to receive intravenous weekly paclitaxel at 50mg/m2/dose concurrent with XRT (5040 cGy in 28
fractions) and oral glutamine 10g three times daily. Patients were re-evaluated following the completion of combined modality treatment (CMT), restaged, and then underwent resection. Patients with initial clinical stage T3 or N+ tumors were offered adjuvant chemotherapy. Clinical data was collected during the treatment regimens preoperatively and postoperatively to evaluate for tumor response, toxicity of treatment as well as to compare variations and/or complications of the surgical procedure. Patients were followed after therapy for evaluation of recurrence or cure, toxicity symptoms and quality of life.

**Results**

Enrollment goal was met with 25 patients (9 female and 16 male) and data are presented here. Of the 25 patients enrolled in this study, we report the findings on 24 evaluable patients. The median age was 58 years (range 40-83). There were 15 distal rectal (≤ 5 cm above anal verge) and 9 mid-upper rectal lesions. These included 7 well differentiated, 8 moderately differentiated and 3 poor or undifferentiated adenocarcinomas. Differentiation of the remaining 6/24 (25%) was not stated in pathology record. Initial staging information was missing from 2/24 evaluable patient records. Initial T stage was T2 in 1 (4.5%), T3 in 20 (91%) and T4 in 1 (4.5%) of 22 patients. Initial imaging used for staging could not assess nodal status in 5/22 patients. Initial N stage was N- in 10/17 (59%), N+ in 7/17 (41%). All patients were M0. Twenty-three of 24 (96%) planned doses of paclitaxel were administered and 23/24 (96%) patients received the full dose of XRT. Toxicity was graded per SWOG criteria. Adverse effects during preoperative chemoradiotherapy included hematologic toxicity: 11 patients with grade 1 or 2 anemia, 1 patient with grade 3 anemia, 3 patients with grade 1 or 2 neutropenia, 1 patient with grade 3 neutropenia (these included 1 patient with both grade 1 anemia and grade 2 neutropenia). Fourteen patients had grade 1 or 2 diarrhea, 2 had grade 3 and 2 had grade 4. Grade 1 or 2 dysuria occurred in 8 patients. Perianal erythema/desquamation was grade 1 or 2 in 14 patients and grade 3 in 4.

Twenty-two of 24 (92%) patients were surgically resected. One patient had distant metastases found on presurgical imaging and another died from his disease prior to completing the neoadjuvant regimen. Two surgically resected patients had microscopic (+) margins. Low anterior resection was accomplished in 17/22 (77%) and 5/22 (23%) patients required abdominoperineal resection. Two patients experienced postoperative fever and 8 experienced wound complications including infection, hernia or fistula. One patient experienced a postoperative small bowel obstruction requiring surgical intervention. While in the immediate postoperative recovery period, 5 patients experienced mild to moderate fecal incontinence, tenesmus and/or diarrhea all of which eventually resolved.

Final pathologic stage was Tis/T1 in 4 (18%), T2 in 5 (23%) and T3 in 13 (59%) of 22 patients; N- in 15/22 (68%), N+ in 7/22 (32%). Three of 23 (13%) progressed to metastatic disease prior to surgery. Of 15 patients with evaluable T and N staging at
both enrollment and at surgery there was 1 (7%) pathologic complete response (CR). Of 20 patients with evaluable T staging at both enrollment and at surgery, there were 2 (10%) T stage CRs; of 15 patients with evaluable N staging there were 2 (13%) N stage CRs. Twenty of 24 (83%) patients received postoperative 5-FU-based chemotherapy. One patient with a down-staged T2N0M0 tumor elected not to proceed with postoperative adjuvant therapy.

With a median follow-up of 89 months (7.5 yrs), 14/22 (64%) patients remained disease-free after treatment. Two patients died of intercurrent disease and 12 are still living. Eleven of those still living have exceeded their 5-year mark disease-free. Five year disease-free survival is 64% and 5 year overall survival is 76%. Median current disease-free survival is 5.0 years and median overall survival is 6.4 years. One patient who experienced pathologic recurrence of their disease is also still living with overall survival of more than 9 years.

**Conclusions** -
This study offers the benefit of a prospective, phase 2 trial of paclitaxel as a preoperative neoadjuvant chemotherapeutic agent in the setting of primary rectal cancer. Results show paclitaxel to be tolerable when compared to the current neoadjuvant regimen of infusional 5-FU delivered concurrently with XRT. Paclitaxel does not lead to an increase in postoperative complications compared to current standard of care regimens. With regard to potential preservation of anal sphincter function, paclitaxel showed 7/19 (37%) overall down-staging and 3/14 (21%) pathologic down-grading. There was a 9/20 (45%) reduction in T stage and 1/15 (7%) pathologic CR (T and N stage) of the primary tumor. We believe that this data is sufficient to support the use of paclitaxel as a safe alternative to either 5-FU or oral chemotherapeutic agents in patients who cannot tolerate them.

We hope to update this analysis with comparison of paclitaxel to the current standard of care in neoadjuvant chemoradiotherapy and also to currently acceptable alternative therapies. In addition we hope to provide descriptive information with respect to the treatment, complications and outcomes of these patients so that overall management and patient quality of life may be optimized. Additionally, there is ongoing evaluation of other clinical data from this trial including a quality of life questionnaire as well as the presence or absence of the p53 mutation from initial biopsies and surgical resection specimens. We believe these analyses will aid in the current knowledge and consideration of alternative therapeutic options as well as understanding the possible treatment outcomes of patients with clinically localized rectal cancer.
References-