Original Article

Adjuvant FOLFOX Treatment for Stage III Colorectal Cancer: Why Patients Quit FOLFOX?

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Key Words
Colorectal cancer;
Adjuvant chemotherapy;
FOLFOX

Purpose. Adjuvant FOLFOX chemotherapy is the standard treatment for stage III colorectal cancer. However, most patient failed to complete full course. This study aimed to evaluate the completion rate and reasons for not fulfilling.

Materials and Methods. This is a retrospective observation cohort study. Cases of stage III colorectal adenocarcinoma underwent curative resections and adjuvant FOLFOX chemotherapy between January 2009 and December 2015 were retrieved from the section of colorectal surgery database at Taipei Veterans General Hospital. Basic data of patient were collected including the reason of quitting FOLFOX, and the cumulative dose of oxaliplatin.

Results. A total of 886 consecutive cases of stage III colorectal cancer were initially found. 110 cases were excluded due to refusing adjuvant chemotherapy, 199 receiving other regimen, 5 treating at other hospital. 572 patients were analyzed. 290 (50.6%) completed 12 cycles treatment with median Oxaliplatin cumulative dose of 984 mg/m^2 (644~1210 mg/m^2). Among the 282 patients that failed to complete the treatment, 78 (27.7%) patients were due to physician's protectively early termination, 72 (25.5%) peripheral neuropathy, 30 (10.6%) disease progression, 18 (6.4%) allergic to oxaliplatin, 19 (6.7%) neutropenia, or deteriorated liver/kidney function, 17 (6.0%) severe nausea/vomiting, 12 (4.3%) deteriorated general condition, and 36 (12.8%) patient's request. For those quitted due to neuropathy, the median cumulative dose of oxaliplatin is 746 mg/m^2, and 680.4 mg/m^2 for allergic reaction.

Conclusions. Half of patients completed full course adjuvant FOLFOX. Preventive termination and peripheral neuropathy are the main reasons for quitting. Therapy to prevent or ameliorate Oxaliplatin-related neuropathy is needed to improve the completion rate.

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For stage III colon cancer, 12 cycles of FOLFOX (folinic acind (leucovorin), flurouracil, and oxaliplatin) became the standard adjuvant chemotherapy regiment (ACR) according to beneficial results obtained in Multicenter International Study of oxaliplatin/5-fluorouracil/leucovorin in ajuvant treatment

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of colon cancer (MOSAIC) trial in 2004,[1] and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 report in 2007.[2] However, the completing rate (74.7%) of full course in MOSAIC study was not so high.[1] A recent retrospective cohort study of 19 veteran medical centers in USA even reported a lower rate of 58.2%.[3] Inadequate adjuvant dosage might affect the expected benefit of FOLFOX.

Recent study comparing 3 months and 6 months of adjuvant chemotherapy (Randomized trial investigating the role of FOLFOX-4 or XELOX (3 versus 6 months) regimen duration and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer (Tosca Trial) revealed better compliance and tolerance of 3 months of treatment compared with 6 months,[4] but the impact on survival was not known yet. However, our previous retrospective study revealed significant overall survival improvement after 8 cycles of FOLFOX treatment,[5] but this outcome will be tested in the TOSCA trial.

In this study, we intended to study the completing rate of adjuvant ACR FOLFOX in our hospital, and also the reasons why patients quit.

Methods

This is a retrospective observation cohort study of patients treated between January 2009 and December 2015. Cases were retrieved from the colorectal surgery database at Taipei Veterans General Hospital. Cases of stage III colorectal adenocarcinoma undergoing curative resections and ACR FOLFOX chemotherapy were retrieved. Patients received neoadjuvant radiotherapy were included. All patients signed informed consents to be enrolled into the database. Right side colon was defined from cecum to splenic flexure, left side as descending and sigmoid colon. This study was approved by the Local Survey and Behavior Ethics Committee (TPEVGH IRB No. 2016-12-011CC).

Statistical analysis

General clinicopathological data were collected for analyses, including age, gender, pre-operative carcinoembryonic antigen (CEA), pT and pN staging, tumor site, harvested lymph node number (cutoff number, 12), ECOG performance, and interval between surgery and ACR (cutoff, 8 weeks). Statistical analyses were performed using SPSS, version 22 (IBM Corp. Armonk, New York, USA). Significance was set at $p < 0.05$.

Result

A total of 886 consecutive cases of stage III colorectal cancer were initially found in the section of colorectal surgery database at Taipei Veterans General Hospital. Among them, 110 cases were excluded due to refuse adjuvant chemotherapy, the other 199 for received ACR other than FOLFOX, and another 5 receiving ACR in other hospital. As a result, 572 cases were analyzed. Table 1 showed demographic data. Among the study population of median age 62.0 years old, there was a predominant distribution of males (58.7%), pT1~T3 (82.5%), pN1 (63.1%), low preoperative CEA (< 5 ng/ml; 64.0%), and left side colon localization (41.8%). There were also high rates of well- or moderately differentiated tumors (86.7%), receiving ACR within 8 weeks after operation (95.8%), more than 12 lymph nodes harvested (90.9%), and with ECOG performance status grade of 0 (87.9%).

Only about half of the study population (290, 50.6%) finished 12-cycle treatment, with median oxaliplatin cumulative dose of 984 mg/m^2 (range, 644~1210 mg/m^2). Among the 282 cases without completing, 205 (72.7%) receiving other 5-FU based replacement ACR (High Dose 5-Flourouvacil (HDFL), Ufur, or FOLFIRI). Further exploring into the reasons why quitting was performed (Fig. 1): 78 (27.7%) cases due to physicians' planned early termination, 72 (25.5%) to peripheral neuropathy, 30 (10.6%) to disease progression, 18 (6.4%) to allergic to Oxaliplatin, 19 (6.7%) to neutropenia, or deteriorated liver or kidney function, 17 (6.0%) to severe nausea or vomiting, 12 (4.3%) to deteriorated general condition, and 36 (12.8%) due to cases' requests without an apparent reason. For those who quit due to physicians' planned

Table 1. Demographic data of patients

Sex		
Men	336	58.7%
Woman	236	41.3%
Age (years)		
Median (range)	62.03	20~94
< 70	414	72.4%
≥ 70	158	27.6%
Performance status		
0	503	87.9%
1	58	10.1%
2	11	2.0%
Pathological staging		
pT classification		
pT1~3	472	82.5%
pT4	100	17.5%
pN classification		
pN1	361	63.1%
pN2	211	36.9%
Tumor localization		
Right	158	27.6%
Left	239	41.8%
Rectum	175	30.6%
Obstruction/perforation	35	6.1%
Histology grade		
Well, and moderately differentiated	496	86.7%
Poorly differentiated, undifferentiated	69	12.0%
Missing	7	1.3%
Pre-operative CEA level		
CEA > 5	192	33.7%
CEA ≤ 5	367	64.0%
Missing	13	2.3%
Time to chemotherapy		
≥ 8 weeks	16	2.8%
< 8 weeks	548	95.8%
Missing	8	1.4%
Lymph nodes harvested		
Lymph nodes < 12	52	9.1%
Lymph nodes ≥ 12	520	90.9%

early termination, the median cumulative dose of Oxaliplatin is 505.5 mg/m^2 with mean FOLFOX cycle 6.91. For those who quit due to neuropathy, the median cumulative dose of Oxaliplatin is 746 mg/m^2, and the neuropathy grade is Grade I in 28 cases (39.4%), Grade II in 38 (53.5%), and Grade III in 5 (7.0%), respectively. For those who quit due to allergic reaction, the median cumulative dose of Oxaliplatin is 680.5 mg/m^2, and 14 (77.8%) cases had Grade 2 reaction, as 4 (22.2%) had Grade 3 reaction. No case of Grade 4 reaction was found.

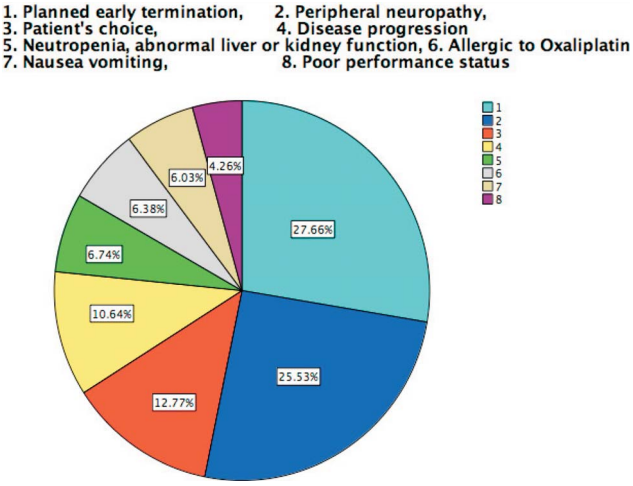

Fig. 1. The reason why patient quitted FOLFOX treatment.

Discussion

Completing rate of full-course FOLFOX is 50.6%, and only 19.6% complete without delay or dose decreased. Planned early termination is the main reason for quitting. It's the physicians' decision to avoid adverse effects, especially the concern of peripheral neuropathy. Of those quitting. 91.8% would further receive continuous HDFL, or oral chemotherapy to fulfill the treatments. Of those quitting truly due to peripheral neuropathy, the median cumulative dose of Oxaliplatin was 746 mg/m^2. Mostly suffered from grade 2 neuropathy. Of those quitting due to allergic reaction, the median cumulative dose was 680.5 mg/m^2, and mostly was grade 2 allergic reaction.

Our completing rate (50.6%) is lower than MOSAIC study (74.7 %),[1] and Japanese JFMC41-1001-C2 (JOIN trial) (67%).[6] However, the recent retrospective cohort study in 19 veteran medical centers in USA revealed similar 58.2% rate in FOLFOX group.[3] National health insurance in our country might play an important role here but need further firm study to confirm. Incompletion group might have negative survival effects, according to our previous survival study in terms of cycle number.[5]

The median cumulative dose of oxaliplatin is 746 mg/m^2 in our quitting due to peripheral neuropathy

group. Reported ratio of peripheral neuropathy varies among different reports. In other clinical trials, sensory symptoms causing functional impairment have been found in only approximately 15% of patients after a cumulative dose of 780~850 mg/m^2 but in 50% of patients at a cumulative dose of 1170 mg/m^2.[7] Recent studies revealed approximately 80% of colorectal cancer patients treated with oxaliplatin alone or in combination with other chemotherapeutics experienced neurotoxicity, and impairment may be permanent.[8-10] Regarding chemotherapy-induced peripheral neuropathies, American Society of Clinical Oncology Clinical Practice Guideline recommended no agents for the prevention.[11] Up to now, treatment modification or withdrawal have been considered the only reliable methods available, even though this cannot guarantee protecting patients from severe peripheral neuropathy, particularly if coasting (progression of symptoms after discontinuation of treatment) occurs.[12]

In addition, for patients quitted due to allergic reaction, the median cumulative dose of Oxaliplatin is 680.5 mg/m^2. In previous studies, the incidence of allergic reactions tended to increase modestly from 5-7 cycles of treatment. Many of grade ≥ 3 allergic reactions developed without the preceding episode of grade-1 or -2 allergic reactions.[13] Our results consisted with these findings. Hypersensitivity may lead to the withdrawal of the chemotherapy, thereby reducing the number of therapeutic options. In previous reports, reintroduction of oxaliplatin is generally possible in grade 1/2 hypersensitive patients using an appropriate premedication strategy: i.e. anti-histamine and/or steroids, and reduced infusion flow.[14] But uniform approach to prevent oxaliplatin allergy has not been established and reintroduction remains associated with recurrence hypersensitivity reaction, which requires permanent withdrawal of oxaliplatin infusion with obvious harmful consequences for the patient. Efforts strengthening prevention are needed.[15]

Of those refusing ACR, they are of older age (79.7 year old, $p < 0.001$), and poorer performance status (PS > 2: 14.7%, $p < 0.001$), compared with receiving FOLFOX. Besides, 199 cases received ACR other than FOLFOX, most adopted oral Ufur or Xeloda. Their age was also older (78.6 year old, $p < 0.001$) than FOLFOX group. In a recent retrospective analysis, only a small incremental survival benefit for patients older than 75 years with stage III colon cancer receiving oxaliplatin containing regimens over non-oxaliplatin regimens.[16] The subset analyses of the MOSAIC trial, patients aged 70~75 years with stage II or III colon cancer showed a lack of survival benefit from the addition of oxalipatin.[17] Besides, the subset analysis of the NSABP C-07 trial found that yield no survival benefit from adding oxalipatin to 5-FU/LV in patients older than 70 years with stage II or III colon cancer, with a trend towards decreased survival (Hazard ratio = 1.18, 95% confidence interval: 0.82~1.62).[18] Our practice matches current trend for old age patient.

This is a single center retrospective cohort study, and the outcomes may have been influenced by unmeasured clinical characteristics and other confounding factors.

Conclusions

Half of patients completed full course adjuvant FOLFOX. Preventive termination and peripheral neuropathy are the main reasons for quitting. Therapy to prevent or ameliorate Oxaliplatin-related neuropathy is needed to improve the completion rate of FOLFOX.

References

1. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer I. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-51.
2. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 2007;25:2198-204.
3. Aspinall SL, Good CB, Zhao X, Cunningham FE, Heron BB, Geraci M, Passero V, Stone RA, Smith KJ, Rogers R, Shields

J, Sartore M, Boyle DP, Giberti S, Szymanski J, Smith D, Ha A, Sessions J, Depcinski S, Fishco S, Molina I, Lepir T, Jean C, Cruz-Diaz L, Motta J, Calderon-Vargas R, Maland J, Keefe S, Tague M, Leone A, Glovack B, Kaplan B, Cosgriff S, Kaster L, Tonnu-Mihara I, Nguyen K, Carmichael J, Clifford L, Lu K, Chatta G. Adjuvant chemotherapy for stage III colon cancer: relative dose intensity and survival among veterans. *BMC Cancer* 2015;15:62.

4. Lonardi S, Sobrero A, Rosati G, Di Bartolomeo M, Ronzoni M, Aprile G, Scartozzi M, Banzi M, Zampino MG, Pasini F, Marchetti P, Cantore M, Zaniboni A, Rimassa L, Ciuffreda L, Ferrari D, Barni S, Zagonel V, Maiello E, Rulli E, Labianca R, Investigators T. Phase III trial comparing 3-6 months of adjuvant FOLFOX4/XELOX in stage II-III colon cancer: safety and compliance in the TOSCA trial. *Ann Oncol* 2016; 27:2074-81.
5. Tsai YJ, Lin JK, Chen WS, Jiang JK, Teng HW, Yen CC, Lin TC, Yang SH. Adjuvant FOLFOX treatment for stage III colon cancer: how many cycles are enough? *Springerplus* 2016; 5:1318.
6. Kotaka M, Yoshino T, Oba K, Shinozaki K, Touyama T, Manaka D, Matsui T, Ishigure K, Hasegawa J, Inoue K, Goto K, Sakamoto J, Saji S, Ohtsu A, Watanabe T. Initial safety report on the tolerability of modified FOLFOX6 as adjuvant therapy in patients with curatively resected stage II or III colon cancer (JFMC41-1001-C2: JOIN trial). *Cancer Chemother Pharmacol* 2015;76:75-84.
7. Grothey A. Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer* 2005;5 Suppl 1:S38-46.
8. Argyriou AA, Briani C, Cavaletti G, Bruna J, Alberti P, Velasco R, Lonardi S, Cortinovis D, Cazzaniga M, Campagnolo M, Santos C, Kalofonos HP. Advanced age and liability to oxaliplatin-induced peripheral neuropathy: post hoc analysis of a prospective study. *Eur J Neurol* 2013;20:788-94.
9. Argyriou AA, Cavaletti G, Briani C, Velasco R, Bruna J, Campagnolo M, Alberti P, Bergamo F, Cortinovis D, Cazzaniga M, Santos C, Papadimitriou K, Kalofonos HP. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. *Cancer* 2013;119:438-44.
10. Argyriou AA, Velasco R, Briani C, Cavaletti G, Bruna J, Alberti P, Cacciavillani M, Lonardi S, Santos C, Cortinovis D, Cazzaniga M, Kalofonos HP. Peripheral neurotoxicity of oxaliplatin in combination with 5-fluorouracil (FOLFOX) or capecitabine (XELOX): a prospective evaluation of 150 colorectal cancer patients. *Ann Oncol* 2012;23:3116-22.
11. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL, American Society of Clinical O. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014;32:1941-67.
12. Cavaletti G, Alberti P, Frigeni B, Piatti M, Susani E. Chemotherapy-induced neuropathy. *Curr Treat Options Neurol* 2011;13:180-90.
13. Sugihara K, Ohtsu A, Shimada Y, Mizunuma N, Lee P, De Gramont A, Goldberg RM, Rothenberg ML, Andre T, Brienza S. Allergic reactions (ARs) induced by FOLFOX4 treatment in colorectal cancer: a comparative analysis between Asian and Western patients (pts). *J Clin Oncol* 2011;29:3623.
14. Yanai T, Iwasa S, Hashimoto H, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Yamamoto H. Successful rechallenge for oxaliplatin hypersensitivity reactions in patients with metastatic colorectal cancer. *Anticancer Res* 2012;32:5521-6.
15. Parel M, Ranchon F, Nosbaum A, You B, Vantard N, Schwiertz V, Gourc C, Gauthier N, Guedat MG, He S, Kiouris E, Alloux C, Vial T, Trillet-Lenoir V, Freyer G, Berard F, Rioufol C. Hypersensitivity to oxaliplatin: clinical features and risk factors. *BMC Pharmacol Toxicol* 2014;15:1.
16. Sanoff HK, Carpenter WR, Sturmer T, Goldberg RM, Martin CF, Fine JP, McCleary NJ, Meyerhardt JA, Niland J, Kahn KL, Schymura MJ, Schrag D. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012;30:2624-34.
17. Tournigand C, Andre T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, Tabernero J, Boni C, Bachet JB, Teixeira L, de Gramont A. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol* 2012;30:3353-60.
18. McCleary NJ, Meyerhardt JA, Green E, Yothers G, de Gramont A, Van Cutsem E, O'Connell M, Twelves CJ, Saltz LB, Haller DG, Sargent DJ. Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database. *J Clin Oncol* 2013; 31:2600-6.

原　著

第三期大腸直腸癌病人無法完成完整術後輔助性 FOLFOX 化學治療之原因分析

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目的　FOLFOX 是第三期大腸直腸癌術後標準輔助性化學治療。但是許多病人無法完成完整療程。本研究欲探討完成完整 FOLFOX 療程的比率及其無法完成的原因。

方法　由台北榮總大腸直腸外科資料庫收集 2009 年一月至 2015 年十二月第三期大腸直腸癌術後接受 FOLFOX 治療之病人之基本資料、接受 Oxaliplatin 之劑量及無法完成之原因做分析。

結果　研究期間內內共 866 個第三期大腸直腸癌病人接受手術。其中 110 人沒有接受後續輔助性化學藥物治療，199 人接受其他療法，5 人於其他他醫院治療。最後收集 572 人分析。290 人 (50.6%) 完成完整療程，其 Oxaliplatin 累計計劑量之中位數為 984 mg/m^2 (644~1210 mg/m^2)。無法完成完整療程的病人中，78 人 (27.7%) 是因為主治醫師預防性停藥，72 人 (25.5%) 因週邊神經病變，30 人 (10.6%) 因疾病進展更換療法，18 人 (6.4%) 因對 Oxaliplatin 過敏，19 人 (6.7%) 因為白血球過低過肝腎功能惡化，17 人 (6.0%) 因嚴重噁心嘔吐，12 人 (4.3%) 因為整體身體狀況變差，36 人 (12.8%) 自行要求停藥。因週邊神經病變而中斷治療的患者，其 Oxaliplatin 的累積劑量中位數為 746 mg/m^2，而因對 Oxaliplatin 過敏中斷治療的患者，其累積劑量中位數為 680.4 mg/m^2。

結論　半數病人能完成完整療程，週邊神經病變及及醫師預防性停藥是無法完成完整療程之主因。研發預防或減緩週邊神經經病變副作用之化學治療方法應能增加完整療程達成率。

關鍵詞　大腸直腸癌、化學治療、FOLFOX。