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## ORIGINAL ARTICLE

# Postoperative Adjuvant 5-Fluorouracil plus Levamisole Chemotherapy for Stage III Colon Carcinoma: 7-Year Experience in a Single Institution

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## ABSTRACT

***Objectives:*** *To determine the therapeutic efficacy and toxicity of 5-fluorouracil plus levamisole as postoperative adjuvant therapy for stage III colon carcinoma, and to identify prognostic variables.*

***Materials and Methods:*** *A retrospective review was undertaken of 168 patients registered in our institution from January 1991 to December 1997 with completely resected stage III colon adenocarcinoma, who received postoperative adjuvant 5-fluorouracil plus levamisole. Data regarding demographics, pathological characteristics, relapse pattern, survival, and treatment toxicity were compiled and analysed.*

***Results:*** *With a median follow-up of 48 months, 72/168 stage III colon carcinoma patients relapsed. Distant metastasis was the predominant mode of failure, with liver being the most common site. 90% of relapses occurred within 3 years of diagnosis. Five-year disease-free survival was 54%. and overall survival was 71%. Grade 3 chemotherapy toxicity was apparent in 0 to 1.8% of patients. No grade 4 toxicity was noted. The most common adverse effect was nausea, followed by thrombocytopenia and diarrhoea. Number of involved nodes and bowel obstruction were independent predictors for disease-free survival. Tumour site, number of involved nodes, and bowel obstruction were independent variables predictive of overall survival.*

***Conclusion:*** *Postoperative adjuvant therapy with 5-fluorouracil plus levamisole is well tolerated and produces favourable outcomes for patients with stage III colon carcinoma. Less nodal involvement and the absence of bowel obstruction are independent positive predictors of disease-free or overall survival, in addition to tumour site.*

***Key Words:*** *Chemotherapy, adjuvant, Colonic neoplasms, Fluorouracil, Levamisole*

## INTRODUCTION

Colon carcinoma represents a significant health problem in Hong Kong. According to the Cancer Registry of Hong Kong in 1997, colon carcinoma ranked second in cancer incidence and third in cancer death for both sexes.[1] Despite curative resection, relapse occurs in a high proportion of patients with stage III colon carcinoma, resulting in poor long-term survival.

Intergroup 0035 is the benchmark trial establishing the adjuvant role of chemotherapy for node-positive colon carcinoma.[2,3] This trial demonstrated a 40% reduction in relapse rate and a 33% decrease in death rate in patients with stage III colon carcinoma receiving postoperative 5-fluorouracil (5-FU) plus levamisole (LEV), as compared with observation or levamisole alone. As a result, a Consensus Panel convened by the National Institutes of Health in 1990 recommended combined 5-FU and levamisole (5-FU/LEV) as standard adjuvant therapy for patients with surgically-treated stage III colon carcinoma.[4]

After the publication of Intergroup 0035, 5-FU/LEV replaced observation as the new control arm for studies on adjuvant chemotherapy for colon carcinoma. Nevertheless, there were few reports on the relapse pattern of patients with stage III colon carcinoma receiving adjuvant 5-FU/LEV. In addition, treatment complications such as hepatic toxicity were not

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comprehensively reported in most trials involving 5-FU/LEV. Furthermore, most of the trials on adjuvant chemotherapy for colon carcinoma were based on a mixed patient population of stages II and III. As a result, the treatment outcome with adjuvant 5-FU/LEV alone for stage III colon carcinoma has not been adequately investigated. Hence, in the present study, data from patients with stage III colon carcinoma receiving postoperative adjuvant 5-FU/LEV in our institution were retrospectively reviewed, specifically focusing on patterns of relapse and survival, and the chemotherapy toxicity profile.

## MATERIALS AND METHODS

### Data Compilation

Patient information was obtained from a database of 647 patients that included all patients with colon carcinoma registered in this institution from January 1991 to December 1997. Patients with pathologically-confirmed node-positive disease (i.e. Stage III, American Joint Committee on Cancer Staging System), who had undergone potentially curative en bloc colectomy with clear margins, and had received adjuvant 5-FU/LEV chemotherapy, were identified.

### Chemotherapy Regimen

5-FU 450 mg/m$^2$ was administered by intravenous (IV) bolus daily for 5 consecutive days in week 1. A weekly IV bolus of 5-FU 450 mg/m$^2$ was initiated at day 29, and continued for 48 weeks. Oral levamisole 50 mg 3 times daily for 3 days was administered, starting on the first day of week 1, and repeated every 2 weeks for 1 year.

### Follow-up Practice

During the chemotherapy course, patients were seen on day 1 and day 15, and then weekly from day 29 onwards. In addition to medical history and physical examination at every visit, serum carcinoembryonic antigen (CEA) level and liver function were assessed every 6 weeks. Chemotherapy toxicity was graded according to WHO criteria. After completion of chemotherapy, patients were seen every 3 to 4 months for the first 2 years, 4- to 6-monthly for years 3 to 5, and then annually. Evaluations consisted of medical history, physical examination, and serum CEA level. Surgical follow-up with regular colonoscopy was arranged.

### Statistical Analysis

Survival was calculated for all patients from the date of first histological diagnosis of colon carcinoma. Survival curves were plotted according to the method of Kaplan and Meier using SPSS software (Windows version 10.0; SPSS Inc., Chicago, United States). Analysis of differences in survival curves was performed by the log-rank test. Multivariate analysis was performed using Cox's proportional hazards model. Backwards stepwise regression was used to assess the variables for the final Cox regression model.

## RESULTS

### Patient Selection and Characteristics

Of the 266 patients identified with node-positive colon carcinoma treated by radical surgery with clear margin, 168 had received adjuvant 5-FU/LEV chemotherapy. Twenty-four patients had received other adjuvant chemotherapy schemes and were not included in the present analysis. Adjuvant chemotherapy was not offered to the remaining 74 patients for the following reasons: patient refusal (7 patients); intercurrent disease (4 patients); elderly (> 70 years) plus poor score (< 70) on Karnofsky Performance Status (KPS) [55 patients]; other reasons (8 patients).

### Clinical and Pathological Characteristics

The clinical and pathological characteristics of these patients are shown in Table 1. The median follow-up for surviving patients was 48 months.

### Relapse

Relapse occurred in 72 of the 168 patients. The pattern of initial relapse was: locoregional relapse alone in 6 patients (3.6%), distant metastasis alone in 52 patients (31.0%), and simultaneous locoregional and distant relapse in 14 patients (8.3%). The most common initial site of distant metastasis was the liver (18/66). Other common sites were lung (15/66), para-aortic node (9/66), and peritoneum (7/66). Twelve patients had multiple initial sites of distant metastasis. For patients relapsing, the median time to relapse was 14.0 months, and 90% of relapses occurred within 3 years of histological diagnosis.

Salvage surgery was performed in 2 of the 6 patients with locoregional relapse alone. The remaining 4 patients received either palliative radiotherapy or symptomatic treatment. Among the 52 patients with distant metastasis alone, 8 patients underwent metastectomy, which was followed by chemotherapy using 5-FU and low-dose leucovorin in 3 patients. Palliative chemotherapy alone was administered in a further 6 patients (5-FU plus low-dose leucovorin in 5 patients, irinotecan/

**Table 1.** Clinical and pathological characteristics in stage III colon carcinoma.

| Clinical and pathological characteristics | No. of patients (%) |
|---|---|
| Age - median (range) | 59.0 (20-76) |
| Sex | |
| Male | 102 (60.7%) |
| Female | 66 (39.3%) |
| Location of primary tumour | |
| Caecum and ascending colon | 35 (20.8%) |
| Flexures and transverse colon | 34 (20.2%) |
| Descending colon | 20 (11.9%) |
| Sigmoid and rectosigmoid colon | 74 (44.0%) |
| Synchronous | 5 (3.1%) |
| T-stage | |
| 1 | 1 (0.6%) |
| 2 | 11 (6.5%) |
| 3 | 106 (63.1%) |
| 4 | 48 (28.6%) |
| Unclear | 2 (1.2%) |
| No. of involved nodes | |
| 1 to 3 | 111 (66.1%) |
| > 3 | 57 (33.9%) |
| Histological differentiation | |
| Well | 23 (13.7%) |
| Moderate | 125 (74.4%) |
| Poor | 12 (7.1%) |
| Unclear | 8 (4.8%) |
| Signet ring cell feature | |
| Yes | 18 (10.7%) |
| No | 150 (89.3%) |
| Circumferential growth | |
| Yes | 81 (48.2%) |
| No | 87 (51.8%) |
| Obstruction | |
| Yes | 37 (22.0%) |
| No | 131 (78.0%) |
| Perforation | |
| Yes | 7 (4.2%) |
| No | 161 (95.8%) |
| Lymphovascular invasion | |
| Yes | 25 (14.9%) |
| No | 143 (85.1%) |

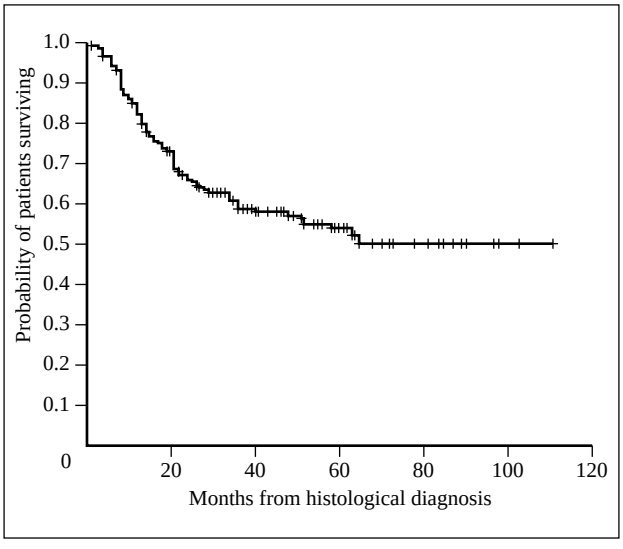


**Figure 1.** Disease-free survival for stage III colon cancer.

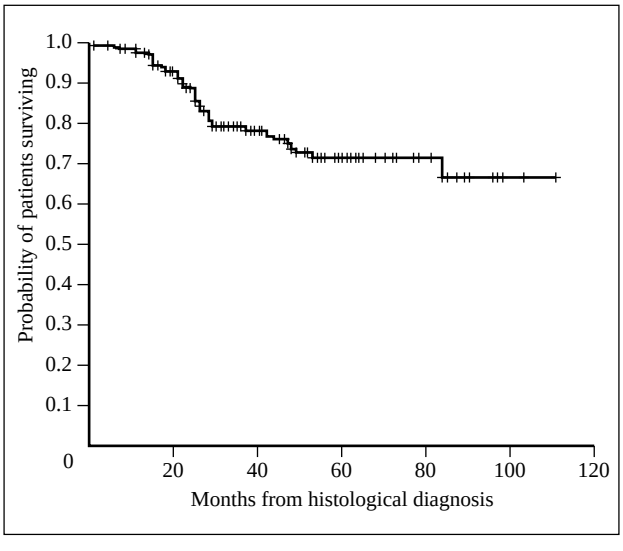


**Figure 2.** Overall survival for stage III colon cancer.

5-FU/leucovorin in 1 patient). Thirty eight patients received symptomatic treatment.

Of the 14 patients with simultaneous locoregional and distant relapse, 2 patients underwent salvage surgery for both local and distant disease. The remaining 12 patients received palliative radiotherapy or chemotherapy, or symptomatic treatment.

## Disease-free Survival

Figure 1 shows the disease-free interval for this group of patients with stage III colon carcinoma. The 5-year disease-free survival rate was 54%.

## Overall Survival

The overall survival curve is shown in Figure 2. The 5-year overall survival rate was 71%. Of the 39 deceased patients, 36 died from recurrent disease and 3 from intercurrent disease.

## Prognostic Factors

Table 2 shows the relationship between the clinical and pathological characteristics and disease-free as well as overall survival. In univariate analysis, tumour site, number of involved nodes, bowel obstruction, and lymphovascular invasion were found to be significant determinants of overall survival, while number of involved nodes and bowel obstruction were significant predictors of disease-free survival. When factors identified as significant in univariate analysis were subjected to multivariate analysis, only tumour site ($p = 0.001$), fewer involved nodes ($p = 0.011$), and absence of bowel obstruction ($p = 0.001$) remained independent prognostic factors for overall survival.

**Table 2.** Prognostic factors for disease-free and overall survival.

| Covariate | No. of patients | Disease-free survival | | Overall survival | |
|---|---|---|---|---|---|
| | | Patients without disease relapse (%) | p value | Patients surviving (%) | p value |
| Age | | | | | |
| <40 | 16 | 68.8 | 0.453 | 81.3 | 0.683 |
| >40 | 152 | 57.9 | | 76.3 | |
| Sex | | | | | |
| Male | 102 | 57.8 | 0.848 | 79.4 | 0.437 |
| Female | 66 | 60.6 | | 72.7 | |
| Tumour sites | | | | | |
| Caecum | 15 | 40.0 | 0.381 | 53.3 | < 0.001 |
| Ascending colon | 20 | 60.0 | | 75.0 | |
| Hepatic flexure | 9 | 66.7 | | 44.4 | |
| Transverse colon | 15 | 73.3 | | 80.0 | |
| Splenic flexure | 10 | 70.0 | | 90.0 | |
| Descending colon | 20 | 55.0 | | 90.0 | |
| Sigmoid colon | 70 | 61.4 | | 82.9 | |
| Rectosigmoid colon | 4 | 50.0 | | 100.0 | |
| Synchronous | 5 | 20.0 | | 20.0 | |
| T-stage | | | | | |
| 1 | 1 | 100.0 | 0.487 | 100.0 | 0.847 |
| 2 | 11 | 72.7 | | 81.8 | |
| 3 | 106 | 54.7 | | 75.5 | |
| 4 | 48 | 60.4 | | 79.2 | |
| Unclear | 2 | 0.0 | | 50.0 | |
| No. of involved nodes | | | | | |
| 1-3 | 111 | 64.0 | 0.023 | 81.1 | 0.022 |
| >3 | 57 | 49.1 | | 68.4 | |
| Histological differentiation | | | | | |
| Well | 23 | 60.9 | 0.7907 | 82.6 | 0.8988 |
| Moderate | 125 | 58.4 | | 76.0 | |
| Poor | 12 | 50.0 | | 75.0 | |
| Unclear | 8 | 75.0 | | 75.0 | |
| Circumferential growth | | | | | |
| Yes | 81 | 61.7 | 0.3569 | 80.3 | 0.2731 |
| No | 87 | 56.3 | | 73.6 | |
| Obstruction | | | | | |
| Yes | 37 | 40.5 | 0.0021 | 62.2 | 0.0015 |
| No | 131 | 64.1 | | 80.9 | |
| Perforation | | | | | |
| Yes | 8 | 58.8 | 0.8735 | 76.9 | 0.9111 |
| No | 160 | 62.5 | | 75.0 | |
| Lymphovascular invasion | | | | | |
| Yes | 25 | 52.0 | 0.0997 | 68.0 | 0.0363 |
| No | 143 | 60.1 | | 78.3 | |

In addition, less nodal involvement ($p = 0.019$) and absence of bowel obstruction ($p = 0.002$) were independent predictors of disease-free survival.

## Toxicity

Gastrointestinal, mucocutaneous, and haematological adverse reactions are summarised in Table 3. These were generally mild, with grade 3 toxicity noted in no more than 1.8% of patients. No grade 4 toxicity was observed. Table 4 summarises the pattern of hepatotoxicity. Hepatic dysfunction without evidence of liver metastasis developed in 61 of the 168 patients. Forty one patients underwent liver ultrasound or abdominal CT scan which excluded liver metastasis. In the remaining 20 patients, all but 1 were disease-free for at least 2 years after the completion of chemotherapy. One patient was found to have lung metastases 6 months after the last dose of chemotherapy, while his liver dysfunction normalised 4 months after the end of chemotherapy. Elevation of 1 liver enzyme occurred in 40 patients (65.6%), of 2 liver enzymes in 14 patients (23%), of 3 liver enzymes in 5 patients (8.2%), and of 3 enzymes together with bilirubin levels in 2 patients (3.2%).

## Treatment Compliance

Of the 168 patients receiving adjuvant chemotherapy, treatment was prematurely terminated in 69 patients at a median of 21 weeks (range, 3 to 49 weeks). The

**Table 3.** Chemotherapy toxicity.

| Toxicity | Grade | Percent of patients |
|---|---|---|
| Gastrointestinal | | |
| Nausea | 0 | 33.9 |
| | 1 | 55.4 |
| | 2 | 10.1 |
| | 3 | 0.6 |
| | – | – |
| Vomiting | 0 | 66.7 |
| | 1 | 25.0 |
| | 2 | 7.1 |
| | 3 | 1.2 |
| | 4 | 0.0 |
| Diarrhoea | 0 | 66.1 |
| | 1 | 28.5 |
| | 2 | 5.4 |
| | 3 | 0.0 |
| | 4 | 0.0 |
| Mucocutaneous | | |
| Stomatitis | 0 | 70.2 |
| | 1 | 26.2 |
| | 2 | 3.6 |
| | 3 | 0.0 |
| | 4 | 0.0 |
| Dermatitis | 0 | 88.7 |
| | 1 | 7.7 |
| | 2 | 2.4 |
| | 3 | 1.2 |
| | 4 | 0.0 |
| Haematological | | |
| Leukopenia | 0 | 75.0 |
| | 1 | 20.2 |
| | 2 | 3.0 |
| | 3 | 1.8 |
| | 4 | 0.0 |
| Thrombocytopenia | 0 | 50.0 |
| | 1 | 42.9 |
| | 2 | 6.5 |
| | 3 | 0.6 |
| | 4 | 0.0 |

overall completion rate was 59%. Disease relapse was the predominant cause for premature termination of adjuvant chemotherapy (35/168), followed by nausea and vomiting (9/168), dermatitis (7/168), haematological toxicity (2/168), psychosocial reasons (2/168), and other reasons (14/168). Excluding patients with disease progression, the compliance rate was 74.4%.

## DISCUSSION

The clinical and pathological characteristics of patients in the present study are similar to those in another local study reported by Wong et al.[5] In both studies, the median age at presentation was in the late 50s, and the male-to-female ratio was 3:2. The predominant histological grade was moderate differentiation. Two-thirds of patients had 1 to 3 involved nodes. The sigmoid colon was the most frequent primary tumour site. A significant proportion of node-positive colon carcinoma patients relapse despite potentially curative surgical resection, resulting in poor long-term survival. The 5-year overall survival for stage III colon carcinoma receiving surgical resection alone has been reported variously as 40% and 56%.[3,6]

The role of 5-FU/LEV postoperative adjuvant chemotherapy in stage III colon carcinoma is well established. Intergroup 0035 demonstrated that 5-FU/LEV produced a significantly higher 5-year relapse-free survival rate of 61% versus 46% with surgery alone, and a significantly higher rate of 5-year overall survival of 65%, compared with 55% for surgery alone.[2,3] The Netherlands Adjuvant Colorectal Cancer Project (NACCP) showed that 5-FU/LEV significantly improved 5-year overall survival as compared with surgery alone in stage III colon carcinoma (56% vs 44%).[7] In the National Surgical Adjuvant Breast and Bowel Project Trial C-04 (NSABP C-04), 5-year disease-free and overall survival rates for the stage III group receiving 5-FU/LEV were 53% and 63%, respectively.[8]

In addition to 5-FU/LEV, a number of other adjuvant chemotherapy regimens for high-risk colon carcinoma have been investigated and utilised clinically in the past 12 years. Most of these are 5-FU based.[2,3,9,10,11] The activity of 5-FU may be either singly modulated by leucovorin, be it high-dose,[10] intermediate-dose,[11] or-low dose,[9] or doubly modulated by leucovorin plus levamisole,[8,12] or leucovorin plus interferon-α.[13]

**Table 4.** Pattern of hepatotoxicity with adjuvant chemotherapy in present trial.

| Hepatic dysfunction | | Percent of patients |
|---|---|---|
| Alkaline phosphatase (ALP) | Raised ALP | 28.6 |
| | ALP > 50% above upper limit of normal range | 6.0 |
| Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)* | Elevated AST | 10.1 |
| | AST > 50% above upper limit of normal range | 4.8 |
| γ-Glutamyl transferase (GGT) | Elevated GGT | 9.5 |
| | GGT > 50% above upper limit of normal range | 6.0 |
| Bilirubin (Bu) | Elevated Bu | 7.1 |
| | Bu > 50% above upper limit of normal range | 3.0 |

* The AST test was replaced by the ALT test from late 1994 onwards.

Comparative studies showed no significant difference among various 5-FU-based adjuvant chemotherapy regimens in terms of overall survival. Intergroup 0089 compared the treatment outcome of 4 different regimens: 5-FU/LEV for 1 year, 5-FU plus high-dose leucovorin (5-FU/HDLV) for 4 cycles, 5-FU plus low-dose leucovorin (5-FU/LDLV) for 6 cycles, and 5-FU plus low-dose leucovorin plus levamisole (5-FU/LDLV/LEV) for 6 cycles. No significant difference in 5-year disease-free survival (56 to 60%) or 5-year overall survival (63 to 67%) was detected among the 4 chemotherapy arms.[12] NSABP C-04, comparing 5-FU/HDLV for 6 cycles with 5-FU/LEV for 1 year, demonstrated no significant difference in 5-year overall survival, while there was a marginally significant difference in 5-year disease-free survival ($p = 0.04$) in favour of 5-FU/HDLV.[8] Similarly, Trial adjCCA-01 compared 5-FU plus intermediate-dose leucovorin (5-FU/IDLV) for 48 weeks with 5-FU/LEV for 48 weeks. This trial showed 5-FU/IDLV to produce 5-year disease-free and overall survival rates superior to those obtained with the abbreviated regimen of 5-FU/LEV used in Intergroup 0035.[14] However, no definitive statement can be made as to whether 5-FU/IDLV for 48 weeks is superior to 5-FU/LEV for 1 year. No significant difference in disease-free or overall survival between 5-FU/LV and 5-FU/LV/interferon-α was observed in NSABP C-05.[13]

In the present study, a 5-year disease-free survival rate of 54%, and 5-year overall survival rate of 71%, were observed with adjuvant 5-FU plus levamisole for 1 year in resected stage III colon carcinoma. These figures are comparable to those cited in previous studies.[3,7,8] Relapse occurred in 72 of 168 patients. Distant metastasis (31.0%) was much more common than locoregional recurrence (3.6%), with the rate of simultaneous locoregional and distant relapse intermediate at 8.3%. Liver was the predominant site of distant metastasis, followed by lung, para-aortic nodes, and peritoneum. A similar pattern of relapse is noted in other studies. Moertel et al reported that 119 of 304 (39.1%) patients with stage III colon carcinoma receiving adjuvant 5-FU plus levamisole developed relapse. Distant failure was much more common than locoregional recurrence. Liver was the leading site of distant metastasis.[2]

Despite the use of various 5-FU-based adjuvant chemotherapy modalities in resected stage III colon carcinoma, relapse-free survival rates of only 53-58%, and 5-year overall survival rates of only 63 to 70% are reported.[3,8] Coupled with the finding that most relapses involve distant metastases, more effective adjuvant systemic therapy is desirable. Irinotecan and oxaliplatin are agents of great promise. Triple therapy regimens using irinotecan/5-FU/leucovorin or an oxaliplatin/5-FU/leucovorin combination have produced encouraging results in metastatic colorectal carcinoma. Compared with the 5-FU/leucovorin combination, they produce significantly better rates of response and of disease-free survival.[15,16] In addition, there has also been significant improvement in overall survival with an irinotecan/5-FU/leucovorin regimen.[16] The adjuvant role of these regimens is currently undergoing investigation. Combined 5-FU/leucovorin/oxaliplatin is a planned investigational arm in the NSABP C-07 trial.[17] In an ongoing intergroup trial, irinotecan/5-FU/leucovorin is being compared with 5-FU/high-dose leucovorin.[18] The results of these trials of adjuvant therapy are eagerly awaited. Table 5 summarises the toxicity profile of

**Table 5.** Toxicity profile of various 5-FU-based chemotherapy regimens in different trials.

| | Percent of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5-FU/LEV* | | | | | 5-FU /HDLV† | | 5-FU /IDLV‡ | 5-FU /LDLV§ | |
| Toxicity ≥ grade 3 | INT 0035 (# 1) | | NSABP-C04 (# 2) | AdjCCA-01 (# 3) | QEH (# 4) | INT 0089 (# 5) | NSABP-C04 (# 2) | IMPACT study (# 6) | INT 0085 (#7) | INT 0089 (#5) |
| | Induction | Maintenance | | | | | | | | |
| Vomiting | 2 | 2 | 2 | 0.6 (nausea + vomiting) | 2 | — | 5 | 2.5 - 10.1 (nausea + vomiting) | — | — |
| Diarrhoea | 3 | 7 | 9 | 1.6 | 0.5 | 30 | 27 | 3.4 - 26.3 | 24 | 21.1 |
| Stomatitis | 5 | 3 | 3-4 | 0 | 0 | 1.4 | 1-2 | 3.4 - 20.7 | 36 | 18.2 |
| Dermatitis | 1 | 1 | — | — | 2 | — | — | — | — | — |
| Leukopenia | 7 | 2 | <2 | 1.6 | 1.5 | 2.8 | — | — | 14 | 11.9 |

* 5-FU/LEV = 5-fluorouracil plus levamisole; † 5-FU/HDLV = 5-fluorouracil plus high-dose leucovorin; ‡ 5-FU/IDLV = 5-fluorouracil plus intermediate-dose leucovorin; § 5-FU/LDLV = 5-fluorouracil plus low-dose leucovorin; (# 1) INT 0035 = Intergroup trial 0035, in which percentage of patients having "severe" toxicity instead of ≥ grade 3 toxicity was reported;[2] (# 2) NSABP C-04 = National Surgical Adjuvant Breast and Bowel Project Trial C-04;[8] (# 3) AdjCCA-01 trial = AdjCCA-01 trial by the Arbeitsgemeinschaft Gastrointestinale Onkologie in North Rhine-Westphalia;[14] (# 4) QEH = Queen Elizabeth Hospital, Hong Kong; (# 5) INT 0089 = Intergroup trial 0089;[12] (# 6) IMPACT study = International Multicentre Pooled Analysis of Colon Cancer Trials;[11] (#7) INT 0085 = Intergroup trial 0085.[9]

various 5-FU-based adjuvant chemotherapy regimens for colon carcinoma, compiled from a number of trials. A higher risk of leucopenia and stomatitis is observed with the 5-FU/LDLV regimen. The 5-FU/HDLV regimen produces the highest incidence of diarrhoea. In general, 5-FU/LEV is associated with the most favourable toxicity profile.

5-FU plus levamisole was well tolerated in the present study. Gastrointestinal, mucocutaneous, and haematological toxicity ≥ grade 3 occurred in fewer than 2% of patients. Furthermore, the toxicity profile of 5-FU/LEV in the present study is comparable with that observed in other adjuvant chemotherapy trials involving 5-FU/LEV for colon carcinoma.[4,8] In view of the similar therapeutic efficacies of the various 5-FU-based adjuvant chemotherapy regimens, and the superior toxicity profile of 5-FU/LEV, 5-FU/LEV should be regarded as one of the optimal choices for adjuvant chemotherapy of resected stage III colon carcinoma.

The pattern of hepatic dysfunction occurring during chemotherapy in the present study is similar to that reported in Intergroup 0035.[19] In both studies, elevation of alkaline phosphatase levels was the most common liver function abnormality, followed by elevated aminotransferase and bilirubin levels. Elevation of γ-glutamyl transferase levels was observed in 7.1% of patients. There have been few reports on completion rates and the causes of premature termination of 5-FU/LEV adjuvant chemotherapy. In Intergroup 0035, treatment was prematurely terminated, at a median of 5 months, in 136/457 (30%) of patients receiving 5-FU plus levamisole. In 56 of these patients (12.3%), toxicity was the principal reason, and the most frequent specific adverse effect was nausea.[2]

In the present study, the overall completion rate of chemotherapy was 99/168 (59%). Of 168 patients, 35 (20.8%) prematurely terminated chemotherapy due to disease progression, while 18 patients (10.7%) prematurely terminated due to adverse effects. Excluding patients with disease progression, the compliance rate was 74.4%. Among the 168 patients, 7 (4.2%) experienced at least 1 category of grade 3 toxicity; in only 3 of these patients was chemotherapy prematurely terminated. In fact, most toxicity-related premature termination of chemotherapy occurred in patients with only grade 1 to 2 toxicity. This apparent paradox can be understood when taking into consideration the duration of toxicity. Due to the prolonged nature and weekly administration schedule of 5-FU/LEV chemotherapy, adverse effects were very frequently of long duration. It is likely that the prolonged adverse effects, although modest in severity, led to premature termination of chemotherapy in some of these patients. Taal et al also commented that, other than recurrence, the most significant reason for the premature termination of 5-FU/LEV chemotherapy was experience of flu-like symptoms and malaise for 1 year.[7]

Regarding prognostic factors, fewer involved nodes and the absence of bowel obstruction were independent predictors of both relapse-free and overall survival. These 2 factors were also identified to be significant independent prognostic indicators of relapse and survival in Intergroup 0035.[2,3] Other reported independent determinants of relapse-free and overall survival in postoperative adjuvant 5-FU/LEV for stage III colon carcinoma are depth of tumour invasion, histological differentiation, and tumour site.[2,3.]

In conclusion, 5-FU/LEV is well tolerated and produces favourable outcomes as surgical adjuvant therapy for patients with stage III colon carcinoma. Tumour site, number of involved nodes, and bowel obstruction are independent prognostic factors for disease-free and overall survival.

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