The History of Colorectal Cancer. What have been achieved over the last 20 years?

June 23, 2018
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Franco-British Institute
Levallois-Perret
Disclosure

Unpaid member of Roche and Sanofi advisory boards
Honorarium Chugai and Yakult
Being old, it’s being young longer than the other.
M1
median survival 6-10 months

Dukes C
5-year survival: 25%

When there was no 5FU...

TABLE XXIV–12–6. Influence of stage of disease on survival after surgical treatment of large bowel cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>81%</td>
</tr>
<tr>
<td>Type B</td>
<td>64%</td>
</tr>
<tr>
<td>Type C</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Includes rectal carcinomas only.
†All large bowel carcinomas.
This invention relates to novel chemical compounds and to novel processes and novel intermediates useful in preparing the same. More particularly, the invention relates to 5-fluorouracil and salts thereof; to methods of preparing said 5-fluorouracil and salts; and to intermediates useful in practicing said methods.
5-Fluorouracil modulation

Response rate benefit

5FU levamisole

5FU PALA

5FU ci

5FU dipyr.

5FU MTX

5FU cisplatin

5FU IFN

LV5FU weekly

FUfol

FUfol low-dose
5FU bolus
Adjuvant Therapy
LEVAMISOLE AND FLUOROURACIL FOR ADJUVANT THERAPY OF RESECTED COLON CARCINOMA

CHARLES G. MOERTEL, M.D., THOMAS R. FLEMING, PH.D., JOHN S. MACDONALD, M.D., DANIEL G. HALLER, M.D., JOHN A. LAURIE, M.D., PHYLLIS J. GOODMAN, M.S., JAMES S. UNGERLEIDER, M.D., WILLIAM A. EMERSON, M.D., DOUGLAS C. TORMEY, M.D., JOHN H. Glick, M.D., MICHAEL H. Veeder, M.D., and JAMES A. MAILLIARD, M.D.*

Abstract Twelve hundred ninety-six patients with resected colon cancer that either was locally invasive (Stage B₂) or had regional nodal involvement (Stage C) were randomly assigned to observation or to treatment for one year with levamisole combined with fluorouracil. Patients with Stage C disease could also be randomly assigned to treatment with levamisole alone. The median follow-up time at this writing is 3 years (range, 2 to 5½).

Among the patients with Stage C disease, therapy with levamisole plus fluorouracil reduced the risk of cancer recurrence by 41 percent (P<0.0001). The overall death rate was reduced by 33 percent (P = 0.006). Treatment with levamisole alone had no detectable effect. The results in the patients with Stage B₂ disease were equivocal and too preliminary to allow firm conclusions. Toxic effects of levamisole alone were infrequent, usually consisting of mild nausea with occasional dermatitis or leukopenia, and those of levamisole plus fluorouracil were essentially the same as those of fluorouracil alone — i.e., nausea, vomiting, stomatitis, diarrhea, dermatitis, and leukopenia. These reactions were usually not severe and did not greatly impede patients’ compliance with their regimen.

We conclude that adjuvant therapy with levamisole and fluorouracil should be standard treatment for Stage C colon carcinoma. Since most patients in our study were treated by community oncologists, this approach should be readily adaptable to conventional medical practice.

There is an adjuvant therapy for colon cancer! The first step (1990)

5-year OS Stage III
1970: 25%
1990: 63%

Figure 3. Survival according to treatment arm. 5-FU = fluorouracil.

Fluorouracil plus Levamisole as Effective Adjuvant Therapy after Resection of Stage III Colon Carcinoma: A Final Report

Charles G. Moertel, MD; Thomas R. Fleming, PhD; John S. Macdonald, MD; Daniel G. Haller, MD; John A. Laurie, MD; Catherine M. Tangen, MS; James S. Ungerleider, MD; William A. Emerson, MD; Douglass C. Tormey, MD, PhD; John H. Glick, MD; Michael H. Veeder, MD; and James A. Mailliard, MD
Adjuvant Therapy (1990-2004)

DFS

6 months = 12 months
Low dose leucovorin
Elderly patients

Francini 1994
IMPACT 1995
NCCTG 1997
NCCTG-NCIC 1998
INT 0089 1998
NSABP C04 1999
QUASAR 2000

5FU bolus + LV

5FU+lev

Moertel

better safety
Adjuvant Therapy

DFS

5FU bolus + LV

X-Act Twelves 2005
NSABPC06 Lambersky 2006

UFT+LV

Capecitabine

LV5FU2/5FU protracted

5FU+lev

UK 2000-2004
INTERGROUP 0153 2000
GERCOR 2003
PETTACC 2

better safety
Small motion or stagnation (1990-2004)

« a decade of decadence »
by Norman Wolmark

New drugs and negative trials
Alpha-interferon
Raltirexed
Edrecolomab targeting cell surface glycoprotein 17-1A
When there was only 5FU….

M+
Median survival 12 months
Stage III
5-year survival 50%
20 years ago...
Summary of Chemotherapy

- Fluopyrimidines single agent first-line achieve up to 30% RR and 6 months PFS
- Oxaliplatin and irinotecan are modestly active as single agent.
- Fluopyrimidines are the backbone of the combination regimens with oxaliplatin and irinotecan
- Doublets 50% RR and 9 months PFS
- Triplet 60% RR and 10 months PFS
- Combination regimens are less active in second-line than in first-line
evolution of a regimen

% / wks

Mayo
LV5FU2
FOLFOX4
FOLFOX6
FOLFIRI
OPTIMOX

RR
PFS
toxicity

1991
1995
1997
2000

20 years ago...
Overall survival

20 years ago…
Multi-Lines

Electrical wires are extension cords!
Stop and Go & Maintenance

Maintenance
Chemotherapy holidays
Algorithm in year 2000

- Surgery
  - CR/PR
    - Stable
      - FOLFOX
      - Stable
        - FOLFIRI
    - PD
      - FOLFIRI
      - PD
        - FOLFIRI

FOLFOX
- Stable
  - FOLFIRI

FOLFIRI
- PR
  - FOLFIRI
- PD
  - FOLFIRI

20 years ago...
Adjuvant Therapy
Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

Thierry André, M.D., Corrado Boni, M.D., Lamia Maanedj-Boudiaf, M.D., Maitz Navarro, M.D., Josep Taberner, M.D., Tamás Hickish, M.D., Clare Topham, M.D., Marta Zannielli, M.D., Philip Clingan, M.D., John Bridgewater, M.D., Isabelle Tabah-Fisch, M.D., Aimery de Gramont, M.D., for the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators

ABSTRACT

Background The standard adjuvant treatment of colon cancer is fluorouracil plus leucovorin (FL). Oxaliplatin improves the efficacy of this combination in patients with metastatic colorectal cancer. We evaluated the efficacy of treatment with FL plus oxaliplatin in the postoperative adjuvant setting.

Methods We randomly assigned 2246 patients who had undergone curative resection for stage II or III colon cancer to receive FL alone or with oxaliplatin for six months. The primary end point was disease-free survival.

Results A total of 1123 patients were randomly assigned to each group. After a median follow-up of 37.9 months, 237 patients in the group given FL plus oxaliplatin had had a cancer-related event, as compared with 293 patients in the FL group (21.1 percent vs. 26.1 percent; hazard ratio for recurrence, 0.77; P=0.002). The rate of disease-free survival at three years was 78.2 percent (95 percent confidence interval, 75.6 to 80.7) in the group given FL plus oxaliplatin and 72.9 percent (95 percent confidence interval, 70.2 to 75.7) in the FL group (P=0.002 by the stratified log-rank test). In the group given FL plus oxaliplatin, the incidence of febrile neutropenia was 1.8 percent, the incidence of gastrointestinal adverse effects was low, and the incidence of grade 3 sensory neuropathy was 12.4 percent during treatment, decreasing to 1.1 percent at one year of follow-up. Six patients in each group died during treatment (death rate, 0.5 percent).

Conclusions Adding oxaliplatin to a regimen of fluorouracil and leucovorin improves the adjuvant treatment of colon cancer.
Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study

Thierry André, Armand de Gramont, Dewi Vernerey, Benoist Chibaudel, Franck Bonnetain, Annemilat Tijeras-Raballand, Aurelie Scriva, Tamas Hickish, Josep Tabernero, Jean Luc Van Laethem, Maria Banzo, Eduard Maartense, Einat Shmueli, Goran U. Carlsson, Werner Scheithauer, Demetris Papanicolaou, Marcus Möehler, Stefania Landolfi, Pieter Demeter, Soudhir Colone, Christophe Tournigand, Christophe Loiues, Alex Duval, Jean-François Fléjou, and Aimery de Gramont
The huge benefit of Oxaliplatin in stage IIIC

Stage III N2
15% absolute benefit

André T et al, JCO 2015
When there was only chemotherapy...

M+
Median survival <24 months
Stage III
5-year survival 75%
Targeted therapies
Targeted therapies and Chemotherapy

First-line Trials
First-line Trials

Bevacizumab phase III 1st line

- IFL N=412
  - RR 35%
  - PFS 6.2 months
  - OS 15.6 months

- IFL Bevacizumab N=403
  - RR 45%
  - PFS 10.6 months
  - OS 20.3 months

- 5FU Bevacizumab N=100
  - RR 40%
  - PFS 8.8 months
  - OS 18.3 months

Hurwitz, NEJM 2004, JCO 2005
First-line Trials

Metastatic CRC: CRYSTAL

- FOLFIRI
- FOLFIRI + Cetuximab

1198 patients

NEJM 2009

RR 38.7%
PFS 8.0 m
OS 18.6 m

RR 46.9%
PFS 8.9 m
OS 19.9 m
First-line Trials

First-line Panitumumab in advanced colorectal cancer PRIME

- FOLFOX4
- FOLFOX4-Pmab

1183 patients

RR 48%
PFS 8.0 months
OS 19.7 months

RR 55%
PFS 9.6 months
OS 23.9 months

Douillard, JCO 2010

1096 KRAS: 656WT
Targeted therapies and Chemotherapy

First-line Trials

FIRE-3: Cetuximab vs Bevacizumab

- FOLFIRI+Bev: RR 58%, PFS 10.3 m, OS 25.0 m, HR 0.77*
- FOLFIRI+Cetux: RR 62%, PFS 10.0 m, OS 28.7 m

Primary endpoint: ORR

First-line
Targeted therapies and Chemotherapy

First-line Trials

CALGB 80405

**Randomisation**

- FOLFOX/FOLFIRI BEV
  - N=559
  - mPFS 10.84m
  - mOS 29.04m

- FOLFOX/FOLFIRI CETUX
  - N=578
  - mPFS 10.45m
  - mOS 29.93m

2334 KRAS WT - mFOLFOX6 73.4% - FOLFIRI 28.6%

Endpoint OS

Venook ASCO 2014
First-line Trials

**Italian Study: TRIBE**

- **FOLFIRI+Bev 12cy → maint.**
  - N=252
- **FOLFOXIRI+Bev 12cy → maint.**
  - N=256

- **Primary endpoint: PFS**

- **N=508 unresectable**
  - Good Pc, median age 60 y

- **RR 53%**
- **PFS 9.7m**
- **OS 25.8m**
- **R0 12%**

- **RR 65%***
- **PFS 12.1m***
- **OS 29.8m***
- **R0 15%**

*Loupakis, Falcone. ASCO GI 2013*

Cetuximab: BOND Trial

EGFR+ tumors refractory to 5-FU/Irinotecan

329/577 screened patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan+ Cetuximab</td>
<td>22.9%</td>
<td>126 d</td>
<td>8.6 months</td>
</tr>
<tr>
<td>Cetuximab → irinotecan</td>
<td>10.8%</td>
<td>45 d</td>
<td>6.9 months</td>
</tr>
</tbody>
</table>

Cunningham, NEJM 2004

The best example of synergy
Afiblercept Second-Line. VELOUR

Randomisation

FOLFIRI + Placebo
N=614

FOLFIRI + Afiblercept
N=612

PFS 6.9 m*
OS 13.5 m*

PFS 4.7 m
OS 12.1 m

Tabernero. ESMO 2011, Van Cutsem JCO 2012

Second-line
REGORAFENIB: CORRECT Trial
Refractory to 5-FU/CPT-11/oxali/Bev/CetuxPmab

RR1.6%
PFS 1.9 m  HR 0.49*
OS 6.4 m  HR 0.77*

RR 0.4%
PFS 1.7 m
OS 5.0 m

Grothey Lancet 2012

3d or 4th-Line
RAISE Ramucirumab

Tumors refractory to 5-FU/oxaliplatin/Bev

FOLFIRI+BSC
RR 12.5%
PFS 4.5m
OS 11.7m

FOLFIRI+RAM
RR 13.7%
PFS 5.7m HR 0.79*
OS 13.3m HR 0.84*

N=1072, primary objective >OS

Second-line Ramucirumab
TAS-102: RECURSE Trial

Third-line

TAS 102
N=534

Placebo
N=266

RR 1.6% NS
PFS 2.0 m HR 0.48*
OS 7.1 m HR 0.68*

RR 0.4%
PFS 1.7 m
OS 5.3 m

Yoshino T. WGIC 2014

Mayer RJ. NEJM 2015
Should we follow mCRC treatment guidelines?

Rationalising the complexity of treatment

Oxaliplatin-based first line
- FOLFOX + Pan or Cet
- FU/Ox
- FU/Ox + Bev
- FU/Iri + Bev
- FOLFIRI + Aflibercept
- Fu/Iri
- FOLFIRI + Pan/Cet
- FU/Iri
- FU/Ox
- FU/Ox + Bev
- FU/Iri + Cet
- FOLFOX + Cet (Pan)
- FU/Iri + Bev
- FU/Ox/Iri
- Pan/Cet ± Iri or FU/Bev

Irinotecan-based first line
- Regorafenib
- Pan/Cet ± Iri
- FU + Bev
- Regorafenib
- Pan/Cet ± Iri
- FU + Bev
- Regorafenib
- Regorafenib
- Regorafenib
- Regorafenib
- Regorafenib
- Regorafenib
Rationalising the complexity of treatment

- Chemo A + Bev
  - PD
  - Chemo B + Bev
    - PD
    - Anti-EGFR
      - PD
      - Regorafenib
### KRAS wt

<table>
<thead>
<tr>
<th></th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Hazard Ratio 95% CI (adjusted*)</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>1.55 (1.32, 1.82)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Cet</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87 (1.48, 2.32)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32 (1.05, 1.65)</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

80405: Sidedness is Prognostic

19.3 MONTHS IS A BIG DIFFERENCE !!

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases

Venook ASCO 2016
« Until that time, only patients whose primary tumors originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease. »
Adjuvant Therapy
New drugs and negative trials
Bevacizumab: NSABP C08 - AVANT
Cetuximab: NO 147 - PETACC8

Subpopulations
Elderly
Stage II

No because of better staging and new biomarkers
For Patients with Dukes’ B (TNM Stage II) Colorectal Carcinoma, Examination of Six or Fewer Lymph Nodes Is Related to Poor Prognosis

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Jean-Philippe Cerottini, M.D.¹
Fred T. Bosman, M.D.²
Michael T. Constanda¹
Jean-Claude Givel, M.D.¹

¹ Department of Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
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BACKGROUND. Lymph node status is pivotal to the staging of colorectal carcinoma. The diagnosis of a lymph node negative tumor should imply a good prognosis; however, the outcomes for Dukes’ B (TNM Stage II) patients remain variable, possibly in part due to understaging. The aim of this study was to determine whether examining a specified minimum number of lymph nodes using conventional techniques would eliminate the risk of understaging and thus have an effect on prognosis.

METHODS. Data on patients who underwent surgery for colorectal carcinoma at a single institution between 1985 and 1990 were reviewed. Patients with Dukes’ B (TNM Stage II) or C (TNM Stage III) tumors and histologically confirmed disease-free resection margins who were treated with curative intent were included. Correlations among variables were assessed using the chi-square test, and survival comparisons were made using Kaplan-Meier curves and the log rank test. Multivariate analysis was performed using a Cox regression model.

RESULTS. Dukes’ B (TNM Stage II) patients with ≤6 lymph nodes examined had significantly poorer overall survival than those with ≥7 lymph nodes examined (P = 0.0014). Such a significant difference was not observed among Dukes’ C (TNM Stage III) patients (P = 0.7). Survival of Dukes’ C patients was significantly worse compared with that of Dukes’ B patients overall and Dukes’ B patients with ≥7 lymph nodes examined (P < 0.0001). There was no significant difference in survival between Dukes’ C and Dukes’ B patients with ≤6 lymph nodes examined (P = 0.02). The number of examined lymph nodes was the only significant parameter correlated with survival in the multivariate analysis (P = 0.002).

CONCLUSIONS. Because Dukes’ B patients with ≤6 examined lymph nodes have poorer outcomes than those with a higher number examined (probably due to understaging), the total number of examined lymph nodes should always be reported. Cancer 1998;83:666–72. © 1998 American Cancer Society.
Left and Right Colon

Survival after relapse

LV5FU2

FOLFOX4

MOSAIC

André A et al. JCO 2015
KRAS/BRAF and MS status

Figure 3. Effect of KRAS and BRAF Status on Disease-Free Survival (DFS) in Patients With Microsatellite-Stable and Microsatellite-Unstable Tumors

A) KRAS status in patients with microsatellite-stable tumors

- MSS KRAS
- MSS BRAF

B) BRAF status in patients with microsatellite-stable tumors

- MSS BRAF

C) KRAS status in patients with microsatellite-unstable tumors

- MSI KRAS
- MSI BRAF

D) BRAF status in patients with microsatellite-unstable tumors

- MSI BRAF

Taieb J et al, JAMA Oncol 2016
Aspirin in mutant PIK3CA

Liao X. NEJM 2012
ct-DNA
Recurrence score
Coloprint
GUCY2C expression in LN
Immunoscore
CDX2
CMS
...
Biomarkers

• We need predictive biomarkers to better define:

1 stage II patients who should be treated
2 stage III patients who should not be treated
3 patients who could benefit from oxaliplatin
4 patients who could benefit from new therapies
IDEA – Meta-Analysis

mFOLFOX6/XELOX

12/8 cycles

mFOLFOX6/XELOX

6/4 cycles

SCOT
N= 3983
TOSCA
N= 2402
GERCOR
N= 2010
CALGB/SWOG 80702
N= 2440
ACHIEVE
N=1291
HORG
N= 708

Non inferiority trial (HR<1.12 – N 10500)
N= 10500  N= 12626
**IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer**

Risk group | Recommended duration of adjuvant therapy
---|---
T1-3 N1 | 3 months
(≈60% of stage III) | 6 months
T4 and/or N2 | (Or other high-risk factors)

Duration of therapy determined by:
- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)

ASCO 2017 Presented by: Qian Shi, PhD on behalf of IDEA collaborators; NEJM 2018
IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

**Risk group**

T1-3 N1

(~60% of stage III)

T4 and/or N2

(Or other high-risk factors)

**Recommended duration of adjuvant therapy**

3 months

6 months

Duration of therapy determined by:
- efficacy of FOLFOX in this setting
- superiority of FOLFOX 12 vs 6 cycles
- non inferiority non demonstrated for CAPOX

Per protocol results

Reassessment when overall survival is mature

ASCO 2017 Presented by: Qian Shi, PhD on behalf of IDEA collaborators; NEJM 2018
Primary DFS Analysis (mITT)

### Duration 3-yr DFS

<table>
<thead>
<tr>
<th>Duration</th>
<th>3-yr DFS</th>
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<tbody>
<tr>
<td>3m</td>
<td>74.6 %</td>
</tr>
<tr>
<td>6m</td>
<td>75.5 %</td>
</tr>
</tbody>
</table>

**3-yr DFS diff. = -0.9%, 95% CI, (-2.4 to 0.6%)**

**DFS HR = 1.07, 95% CI, 1.00 to 1.1, p= 0.11**

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Shi et al. ASCO 2017, Grothey NEJM 2018
Non Inferiority

Investigator
Statistician

Risk of 3-year recurrence +7%
Risk of 3-year grade 2+ neuropathy -3%
In 2018…
M+
Median survival~30 months
Stage III
5-year survival 85%
New concepts: Evolution and Revolution
New concepts: Evolution and Revolution
New concepts: Evolution and Revolution