| | | | |
|---|---|---|---|
| 4 | エルプラット注射用 100mg | 85(-100) mg/m² | 点滴静注 |
| | ブドウ糖注 5 %250mL | 250 mL | 2 時間 |
| | 3. アイソボリンと同時滴下 | | |
| | 交換サイクル | 2 時間 | |
| 5 | 5-FU注250mg 5 mL | 400 mg/m² | 点滴静注 |
| | 生理食塩液50mL | 50 mL | 0.1時間 |
| 6 | 5-FU注250mg 5 mL | 2400(-3000) mg/m² | 中心静脈(埋込型カテーテル) |
| | 注射用水20mL | 5-FU注と合計93 mL | バクスター LV2 もしくは2day infusor 使用 |
| | | | 22時間 |

在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可.
ナゼア，デカドロンは有害事象対策(推奨).
インフューザー使用時　時間で更新，少量の場合残量破棄，残量が多量の場合主治医に連絡.
終了後自己抜針.
インフューザー総量93ml＝2 ml/h×46時間(92ml)＋ポンプに残る量(1 ml)
(5-FU注250mg 5 mL　400mg/m²
生理食塩液50mL　50mL　は生理食塩水を省きワンショット静注も可.

## 6. mFOLFOX7療法(FOLFOX7 LOHP130mg/m²)

day 1/14

注意点 **血　神　消**

| 投与順 | | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|---|
| day1 | 1 | ナゼア注0.3mg 2 mL | 0.3 mg | ワンショット静脈注射 |
| | | ブドウ糖注 5 %20mL | 20 mL | |
| | 2 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| | 3 | アイソボリン注25mg | 200 mg/m² | 点滴静注 |
| | | ブドウ糖注 5 %250mL | 250 mL | 2 時間 |
| | 4 | エルプラット注射用100mg | 100(-130) mg/m² | 点滴静注 |
| | | ブドウ糖注 5 %250mL | 250 mL | 2 時間 |
| | | 3. アイソボリンと同時滴下 | | |
| | | 交換サイクル | 2 時間 | |
| | 5 | 5-FU注250mg 5 mL | (2400-)3000 mg/m² | 中心静脈(埋込型カテーテル) |
| | | 注射用水20mL | 5-FU注と合計93 mL | バクスター LV2 もしくは2day infusor 使用 |
| | | | | 22時間 |

在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可.
ナゼア，デカドロンは有害事象対策(推奨).
インフューザー使用時　時間で更新，少量の場合残量破棄，残量が多量の場合主治医に連絡.
終了後自己抜針.
インフューザー総量93ml＝2 ml/h×46時間(92ml)＋ポンプに残る量(1 ml)
FOLFOX6の5-FU注のワンショット静脈注射を無くし持続投与の5-FU注を3000mg/m²に増量(Tournigandら)

## 7. PEFG療法

day 1, 8, 15, 22/28(ポンプを用いた抗癌剤投与はday 1-28/28で行われる)

注意点 **血　腎　消　倦**

| 投与順 | | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|---|
| day1 | 1 | ナゼア注0.3mg 2 mL | 0.3 mg | ワンショット静脈注射 |
| | | ブドウ糖注 5 %20mL | 20 mL | |
| | 2 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| | 3 | ランダ注50mg100mL | 40 mg/m² | 点滴静注 |
| | | 生理食塩液500mL | 400 mL | 2 時間 |
| | | | | 遮光 |
| | 4 | ファルモルビシン注10mg | 40 mg/m² | 点滴静注 |
| | | 生理食塩液50mL | 50 mL | 0.1時間 |
| | 5 | ジェムザール注1000mg | 600 mg/m² | 点滴静注 |
| | | 生理食塩液500mL | 500 mL | 1 時間 |

| | | | | |
|---|---|---|---|---|
| | 6 | 5-FU注250mg 5 mL<br>注射用水100mL | 1400(200×7) mg/m²<br>5-FU注と合計84 mL | 中心静脈持続静注(埋込型カテーテル)<br>168時間<br>バクスター7day infuser使用 |
| day8 | 1 | ナゼア注0.3mg 2 mL<br>ブドウ糖注 5 %20mL | 0.3 mg<br>20 mL | ワンショット静脈注射 |
| | 2 | ジェムザール注1000mg<br>生理食塩液500mL | 600 mg/m²<br>500 mL | 点滴静注<br>1時間 |
| | 3 | 5-FU注250mg 5 mL<br>注射用水100mL | 1400(20×7) mg/m²<br>5-FU注と合計85 mL | 中心静脈持続静注(埋込型カテーテル)<br>168時間<br>バクスター7day infuser使用 |
| day15, 22 | | | | |
| | 1 | 5-FU注250mg 5 mL<br>注射用水100mL | 1400(20×7) mg/m²<br>5-FU注と合計85 mL | 中心静脈持続静注(埋込型カテーテル)<br>168時間<br>バクスター7day infuser使用 |

在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可.
CDDPはClイオン存在下でないと不安定となるので生理食塩水で希釈.
アミノ酸製剤等と混注しないこと. CDDP投与中は他の薬剤を一時休止が望ましい.
ナゼア, デカドロンは有害事象対策(推奨).

## 8. S-1/CDDP療法

day 8, 9/35(S-1はday 1-21/35 内服併用)

注意点 **血 腎 消**

| 投与順 | | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|---|
| day8 | 1 | ブドウ糖注 5 %20mL<br>ナゼア注0.3mg 2 mL | 20 mL<br>0.3 mg | ワンショット静脈注射 |
| | 2 | ヴィーンF注500mL<br>デカドロン注 8 mg 2 mL | 500 mL<br>8 mg | 点滴静注<br>2時間 |
| | 3 | 生理食塩液 1 L<br>ランダ注50mg100mL<br>1日1回 | 500 mL<br>70 mg/m² | 点滴静注<br>2時間<br>遮光 |
| | 4 | マンニットール注20%300mL<br>1日1回<br>ランダ終了後 | 300 mL | 点滴静注<br>2時間 |
| | 5 | ヴィーンF注500mL<br>プリンペラ10mg | 500 mL<br>10 mg | 点滴静注<br>2時間 |
| | 6 | ヴィーンF注500mL | 500 mL | 点滴静注<br>2時間 |
| day9 | 1 | ブドウ糖注 5 %20mL<br>ナゼア注0.3mg 2 mL | 20 mL<br>0.3 mg | ワンショット静脈注射 |
| | 2 | ヴィーンF注500mL<br>デカドロン注 8 mg 2 mL | 500 mL<br>8 mg | 点滴静注<br>2時間 |
| | 3 | ヴィーンF注500mL | 500 mL | 点滴静注<br>2時間 |
| | 4 | ヴィーンF注500mL | 500 mL | 点滴静注<br>2時間 |
| 内服<br>day1-21 | | TS-1(20mg or 25mg) | 80-120 mg | 分2 内服<br>8時 20時 |

TS-1をday1-21内服併用
TS-1の量

| | | | |
|---|---|---|---|
| | 体表面積 | ＜1.25m² | TS-1(20mg) 4Cap 80mg 分2 内服 8 時 20時 |
| 1.25m² ≦ | 体表面積 | ＜1.50m² | TS-1(25mg) 4Cap 100mg 分2 内服 8 時 20時 |
| 1.50m² ≦ | 体表面積 | | TS-1(20mg) 6Cap 120mg 分2 内服 8 時 20時 |

CDDPはClイオン存在下でないと不安定となるので生理食塩水で希釈.
アミノ酸製剤等と混注しないこと. TS-1が内服されていることを確認すること(1回量, 1日量, 服薬回数など).
TS-1手帳(日記)の利用を勧める.
day 9は必須ではない.

### 9. low-dose CDDP＋S-1療法

day 1, 4, 8, 11, 15, 18, 22, 25/42(S-1はday 1-28/42 内服併用)

注意点 **消 血 腎**

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | ランダ注10mg20mL | 6-10 mg/m² | 点滴静注 |
| | 生理食塩液100mL | 100 mL | 0.5時間 |
| | TS-1 | 100 mg 分2 | 内服<br>8時 20時 |
| | TS-1をday1-28内服併用 | | |

CDDPはClイオン存在下でないと不安定となるので生理食塩水で希釈．アミノ酸製剤等と混注しないこと．

### 10. WHF肝動注療法

day 1, 8, 15(, 22)/28

注意点 **消 倦**

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | 5-FU注250mg 5 mL | 1500 mg | 肝動注(埋込型カテーテル)<br>動脈注射(肝動脈)<br>5時間 |
| | 生理食塩液250mL | 220 mL | バクスター インフューザーLV50使用 |

在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可．
週1回，増悪を確認するまで継続．休薬する際は3週1休で行うことが多い．

### 11. low-dose FP(LFP)療法

day 1, 4, 8, 11, 15, 18, 22, 25/35(ポンプを用いた抗癌剤投与はday 1-28/35で行われる)

注意点 **消 血**

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| day1, 8, 15, 22 | | | |
| 1 | 5-FU注250mg 5 mL | 1200 mg/m² | 中心静脈持続静注(埋込型カテーテル)<br>168時間 |
| | 注射用水100mL | 5-FU注と合計85 mL | バクスター 7 day infuser使用 |
| 2 | ランダ注10mg20mL | 6 mg/m² | 点滴静注 |
| | 生理食塩液100mL | 100 mL | 0.5時間 |
| day4, 11, 18, 25 | | | |
| 1 | ランダ注10mg20mL | 6 mg/m² | 点滴静注 |
| | 生理食塩液100mL | 100 mL | 0.5時間 |

在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可．
CDDPはClイオン存在下でないと不安定となるので生理食塩水で希釈．
アミノ酸製剤等と混注しないこと．CDDP投与中は他の薬剤を一時休止が望ましい．
インフューザー総量85ml＝0.5ml/h×168時間(84ml)＋ポンプに残る量(1 ml)

### 12. CPT-11療法

day 1/14

注意点 **血 消 倦**

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| day1 1 | ブドウ糖注5％20mL | 20 mL | ワンショット静脈注射 |
| | ナゼア注0.3mg 2 mL | 0.3 mg | |
| 2 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | デカドロン注8 mg 2 mL | 8 mg | 2時間 |
| 3 | ブドウ糖注5％500mL | 500 mL | 点滴静注 |
| | トポテシン注100mg | 150 mg/m² | 1.5時間 |

1-2は有害事象に対する前投薬(推奨)．
開始日より4-5日間CPT-11副作用対策必要．

## 13. CPT-11/CDDP療法

day 1(, 2, )15/28

注意点 血 腎 消 倦

| 投与順 | | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|---|
| day1 | 1 | ブドウ糖注５％20mL | 20 mL | ワンショット静脈注射 |
| | | ナゼア注0.3mg 2 mL | 0.3 mg | |
| | 2 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | デカドロン注 8 mg 2 mL | 8 mg | 2 時間 |
| | 3 | ブドウ糖注５％ 500mL | 500 mL | 点滴静注 |
| | | トポテシン注100mg 5 mL | 70 mg/m² | 1.5時間 |
| | 4 | 生理食塩液１L | 500 mL | 点滴静注 |
| | | ランダ注50mg100mL | 80 mg/m² | 2 時間 |
| | | 1日1回 | | 遮光 |
| | | トポテシン終了後 | | |
| | 5 | マンニットール注20％300mL | 300 mL | 点滴静注 |
| | | 1日1回 | | 2 時間 |
| | | ランダ終了後 | | |
| | 6 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | 1日1回 | | 2 時間 |
| | 7 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | 1日1回 | | 2 時間 |
| day2 | 1 | ブドウ糖注５％20mL | 20 mL | ワンショット静脈注射 |
| | | ナゼア注0.3mg 2 mL | 0.3 mg | |
| | 2 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | デカドロン注 8 mg 2 mL | 8 mg | 2 時間 |
| | 3 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | 1日1回 | | 2 時間 |
| | 4 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | 1日1回 | | 2 時間 |
| day15 | 1 | ブドウ糖注５％20mL | 20 mL | ワンショット静脈注射 |
| | | ナゼア注 0.3mg 2 mL | 0.3 mg | |
| | 2 | ヴィーンF注500mL | 500 mL | 点滴静注 |
| | | デカドロン注 8 mg 2 mL | 8 mg | 2 時間 |
| | 3 | ブドウ糖注５％ 500mL | 500 mL | 点滴静注 |
| | | トポテシン注100mg | 70 mg/m² | 1.5時間 |

1-2は有害事象に対する前投薬(推奨).
開始日より4-5日間制吐剤内服およびCPT-11副作用対策必要.
day2は必須ではない.

## 14. CPT-11/CDDP 24時間持続静注療法

day 1, 8, 15/21

注意点 血 倦

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | ブドウ糖注５％100mL | 100 mL | 0.5時間 |
| 2 | トポテシン(カンプト)注40mg 2 mL | 60 mg | 中心静脈(埋込型カテーテル) |
| | ランダ注 10mg20mL | 10 mg | バクスター シングルデイインフューザー使用 |
| | 生理食塩液50mL | | |
| | トポテシン(カンプト)注, ランダ注と全量49mL | | 24時間 |

1は前投薬(必ずしも必須でない).
在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可.
CDDPはCPT-11との混注では活性が落ちないが, デカドロンとの混注では活性が低下するので混注しない.
インフューザー総量49ml＝2 ml/h×24時間(48ml)＋ポンプに残る量(1 ml)

### 15. CPT-11 24時間持続静注療法

day 1, 8, 15/21

注意点 倦 血

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| 2 | トポテシン(カンプト)注40mg 2 mL | 40(-80) mg | 中心静脈(埋込型カテーテル) |
| | 生理食塩液50mL トポテシン(カンプト)注と全量49 mL | | バクスター シングルデイインフューザー使用 |
| | | | 24時間 |

1は前投薬(必ずしも必須でない).
在宅化学療法加算1500点＋携帯型ポンプ加算2500点算定可.
インフューザー総量49ml＝2 ml/h×24時間(48ml)＋ポンプに残る量(1 ml)

### 16. weeklyPTX療法(点滴前処置)

day 1, 8, 15/21

注意点 血 脱 神

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | ナゼア注0.3mg 2 mL | 0.3 mg | 静注 |
| | ブドウ糖注 5 %20mL | 20 mL | |
| 2 | ガスター注20mg | 20 mg | 静注 |
| | ブドウ糖注 5 %20mL | 20 mL | |
| 3 | ポララミン注 5 mg 1 mL | 5 mg | 点滴静注 |
| | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| 4 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| 5 | パクリタキセル注30mg 5 mL | 60-80 mg/m² | 点滴静注 |
| | 生理食塩液 250mL | 250 mL | 専用点滴set使用 |
| | | | 1 時間 |

1-4はアレルギー反応などに対する前投薬(2-4は必須).
PTXは通常の点滴セットの場合，可塑剤が溶け出すので専用点滴セット使用のこと.
PTXは薬液中にアルコールを含有するため注意が必要.

### 17. DTX療法(前処置あり)

day 1/21

注意点 血 脱 神

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | ナゼア注 0.3mg 2 mL | 0.3 mg | 静注 |
| | ブドウ糖注 5 %20mL | 20 mL | |
| | 1日1回 | | |
| 2 | ガスター注20mg | 20 mg | 静注 |
| | 生理食塩液20mL | 20 mL | |
| | 1日1回 | | |
| 3 | ポララミン注 5 mg 1 mL | 5 mg | 点滴静注 |
| | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| | 1日1回 | | |
| 4 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| | 1日1回 | | |
| 5 | ドセタキセル注80mg 2 mL<溶解液付> | 60 mg/m² | 点滴静注 |
| | 生理食塩液250mL | 250 mL | 1時間 |
| | 1日1回 | | |

1-4はアレルギー反応などに対する前投薬(必ずしも必須ではない).
DTXは添付の溶解液中にアルコールを含有するため注意が必要.

## 18. CPT-11/LV/FU(IFL)療法

day 1, 8/21

注意点 血 脱 消 倦

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | ナゼア注0.3mg 2 mL | 0.3 mg | 静注 |
| | ブドウ糖注 5 %20mL | 20 mL | |
| 2 | デカドロン注 8 mg 2 mL | 8 mg | 点滴静注 |
| | ブドウ糖注 5 %100mL | 100 mL | 0.5時間 |
| 3 | アイソボリン注25mg | 10 mg/m² | 点滴静注 |
| | 生理食塩液50mL | 50 mL | 0.1時間 |
| | 1日1回 | | |
| 4 | 5-FU注250mg 5 mL | 500 mg/m² | 点滴静注 |
| | 生理食塩液50mL | 50 mL | 0.1時間 |
| | 1日1回 | | |
| 5 | トポテシン(カンプト)注100mg 5 mL | 100 mg/m² | 点滴静注 |
| | 生理食塩液250mL | 250 mL | 1.5時間 |
| | 1日1回 | | |

1-2は前投薬(必ずしも必須ではない). 骨髄抑制, 下痢などの有害事象に注意が必要.
3, 4 はワンショット静注も可.

## 19. LV/FU(RPMI)療法

day 1, 8, 15, 22, 29, 36/56

注意点 消 倦

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| 1 | ナゼア注0.3mg 2 mL | 0.3 mg | 静注 |
| | ブドウ糖注 5 %20mL | 20 mL | |
| 2 | アイソボリン注 25mg | 250 mg/m² | 点滴静注 |
| | KN補液3B注500mL | 500 mL | 2 時間 |
| 3 | 5-FU注250mg 5 mL | 500-600 mg/m² | アイソボリン開始 1 時間後点滴静注 |
| | 生理食塩液50mL | 50 m | |

1 は前投薬(必ずしも必須でない).
5-FU (adjuvant時 500mg/m² / 進行再発 600mg/m²) で使用されることが多い.
3 は生理食塩水を省きワンショット静注も可.

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# A phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma

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## Abstract

**Background:** Unresectable biliary tract carcinoma is known to demonstrate a poor prognosis. We conducted a single arm phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) for advanced biliary tract malignancies basically on an outpatient basis.

**Methods:** Between February 1996 and September 2003, 42 patients were enrolled in this trial.

**LFP therapy:** By using a total implanted CV-catheter system, 5-FU (160 mg/m$^2$/day) was continuously infused over 24 hours for 7 consecutive days and CDDP (6 mg/m$^2$/day) was infused for 30 minutes twice a week as one cycle. The administration schedule consisted of 4 cycles as one course. RESIST criteria (Response evaluation criteria for solid tumors) and NCI-CTC (National Cancer Institute-Common Toxicity Criteria) (ver.3.0) were used for evaluation of this therapy. The median survival time (MST) and median time to treatment failure (TTF) were calculated by the Kaplan-Meier method.

**Results:** Patients characteristics were: mean age 66.5(47–79): male 24 (54%): BDca (bile duct carcinoma) 27 GBca (Gallbladder carcinoma) 15: locally advanced 26, postoperative recurrence 16. The most common toxicity was anemia (26.2%). Neither any treatment related death nor grade 4 toxicity occurred. The median number of courses of LFP Therapy which patients could receive was two (1–14). All the patients are evaluable for effects with an over all response rates of 42.9% (95% confidence interval C.I.: 27.7–59.0) (0 CR, 18 PR, 13 NC, 11 PD). There was no significant difference regarding the anti tumor effects against both malignant neoplasms. Figure 2 Shows the BDca a longer MST and TTF than did GBca (234 vs 150, 117 vs 85, respectively), but neither difference was statistically significant.

The estimated MST and median TTF were 225 and 107 days, respectively. The BDca had a longer MST and TTF than GBca (234 vs 150, 117 vs 85, respectively), but neither difference was statistically significant.

**Conclusion:** LFP therapy appears to be useful modality for the clinical management of advanced biliary tract malignancy.

## Background

Biliary tract cancers are rare in North America, with approximately 8,000 new cases diagnosed in 2003 [1]. However, bile duct carcinoma (BDca) and gallbladder carcinoma (GBca) are not rare in northern Japan [2], Taiwan [3], and South Korea [4]. In Japan, these malignancies are the sixth leading cause of cancer deaths, and in 1999, there were 8,557 deaths from BDca and 6,340 deaths from GBca [5]. As an surgical resection of the primary tumor and the areas of local extension remains the most effective therapy [6], even for non-curative operations [7]. However, in over 75% of the patients whose disease is locally advanced or already metastatic cases, the median survival time for patients receiving only the best possible supportive care is only about 6 months [1]. Furthermore, there is a high rate of both local and systemic recurrence, even after a curative resection [1,6]. As a result, an effective chemotherapy for biliary malignancy has been eagerly awaited. However, systemic single-agent chemotherapy has so far shown a poor efficacy [6,8], though many efforts has been done [9]. For example, the response rate of 5-fluorourasil (5-FU), cisplatin (CDDP), was 10–13%, and 8%, respectively [4], while new chemotherapeutic agents CPT-11, Gemsitabine, showed the poor response rate of 12.5% and 8%, respectively [3,4,10].

As a result, an effective combination chemotherapy has been eagerly anticipated. We spotlighted the combination of the two old anti-cancer agents, 5-FU, and CDDP.

In Japan, FP therapy combination of 5-FU continuous venous infusion (CVI) and low-dose consecutive CDDP (LFP) Therapy has been widely used since early 1990s for gastrointestinal advanced cancer [11,12]. Because of its low toxicity and relatively high response rate [13], LFP therapy has been widely used for the treatment of various unresectable advanced solid tumors, such as gastric cancer [14], hepatocellular carcinoma [15], pancreatic cancer [12], colon and head and neck [11]. Recent findings in experimental models have shown an additive or synergistic antitumor effects of LFP therapy. We observed that CDDP inhibited metionine transport into tumor cells, both in vitro and in vivo, with a synergic interaction by CDDP functioning as a modulator of 5-FU [11,12]. This synergistic effect was also associated with the induction of apoptosis [16] and the p53 pathway [17,18].

Based on these findings, we conducted a single arm phase II study of LFP therapy in patients with advanced BDca and GBca.

## Methods

### *Eligibility criteria*

This study protocol was approved by the Kochi Municipal Central Hospital, Japan and written informed consent was obtained from all the patients. The patients were required to have unresectable locally advanced or metastatic disease of the biliary-tract or gallbladder advanced carcinoma with measurable lesions on a computed tomography (CT) scan. Other eligibility criteria included an age 18 years or more, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, estimated life expectancy of 12 weeks or more, adequate bone marrow function (leukocyte count > 3,500/μl, neutrophil count > 1,500/μl, and platelet count > 100,000/μl), bilirubin < 5.0 mg/dl, transaminases and alkaline phosphatase < 6 times upper limit of normal, and normal renal function tests (creatine level < 1.5 mg/dl, or creatinine clearance > 60 ml/min). No previous chemotherapy was permitted within 2 weeks. Radiotherapy and stenting to decompress the biliary tract was permitted. Patients with other clinically significant laboratory abnormalities, uncontrolled infection, concurrent severe medical problems unrelated to malignancy that would expose the patient to extreme risk, patients receiving another investigational drug within 30 days prior to study or receiving concurrent hormonal therapy, immunotherapy and those pregnant or lactating were excluded from the study. The study was conducted according to the Good Clinical Practices and the Declaration of Helsinki as amended in Hong Kong (1989).

### *Treatment plans*

All patients were admitted to the hospital for about 10 days for a pretreatment evaluation, the first cycle treatment, and observation for adverse effects. If the degree of toxicity was within Grade 0–2, a second cycle of treatment or more were continued on an outpatient basis.

A pretreatment evaluation included complete medical history, physical examination, evaluation of performance status, urinalysis, chest radiograph, and diagnostic studies assessment such as CT scan. When the patient meets the eligibility criteria, central venous catheter system with a heparin coated catheter (Anthron PU catheter; TORAY™ and a port (Celcite brachial; TORAY™ or Vital port mini; COOK™) is implanted according to the method of Hata et al [19] prior to treatment.

The treatment plan involved the administration of 5-FU (160 mg/m$^2$/day) was continuously infused over 24 hours using a disposable infusion pump (7-day Infuser; Baxter™) and CDDP (3–6 mg/m$^2$/day) diluted with normal serine was infused for half an hour. Hydration was not needed. These doses were determined based on our experience of the previous LFP therapy for hepatocellular carcinoma [15]. The administration schedule consisted of 5-FU for 7 consecutive days and CDDP twice a week (day 1 and day 4) for each of four weeks as one treatment course. The treatment schedule and CV catheter system was

depicted on figure 1. Unless an exacerbation of the symptoms was observed, multiple courses of treatment were administered. When more than a grade 3 adverse effect was observed, a CDDP infusion was omitted and observed. If this omission was ineffective, 5-FU was also omitted. In case of hemoglobin < 8.0 g/dl, platelet count < 50,000/μl neutrophil count < 1,000/μl, blood transfusion of concentrated red blood cells (RBCs) or platelets, or granulocyte-stimulating factor (G-CSF) was applied.

We do not increase the dose of the anti-cancer agent during the chemotherapy protocol, even if the toxicity is low.

### *Toxicity and response evaluation*

Complete blood counts twice a week and biochemical examinations were weekly carried out. Toxicity was evaluated based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) ver.3. The response was classified based on the Response Evaluation Criteria in Solid Tumors Guidelines (RECIST 'criteria) [20], taking into account the measurement of the longest diameter only for all target lesions: complete response (CR)-the disappearance of all target lesions; partial response (PR)-at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease (PD) -at least a 20% increase in the sum of the longest diameter of target lesions, taking as referenve the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; no change (NC)-neither sufficient shrinkage to quality for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started. Patients with a CR, a PR, an NC, or a PD required a confirmatory disease assessment at least one

Figure 1. *Schedule for treatment and infusional method*

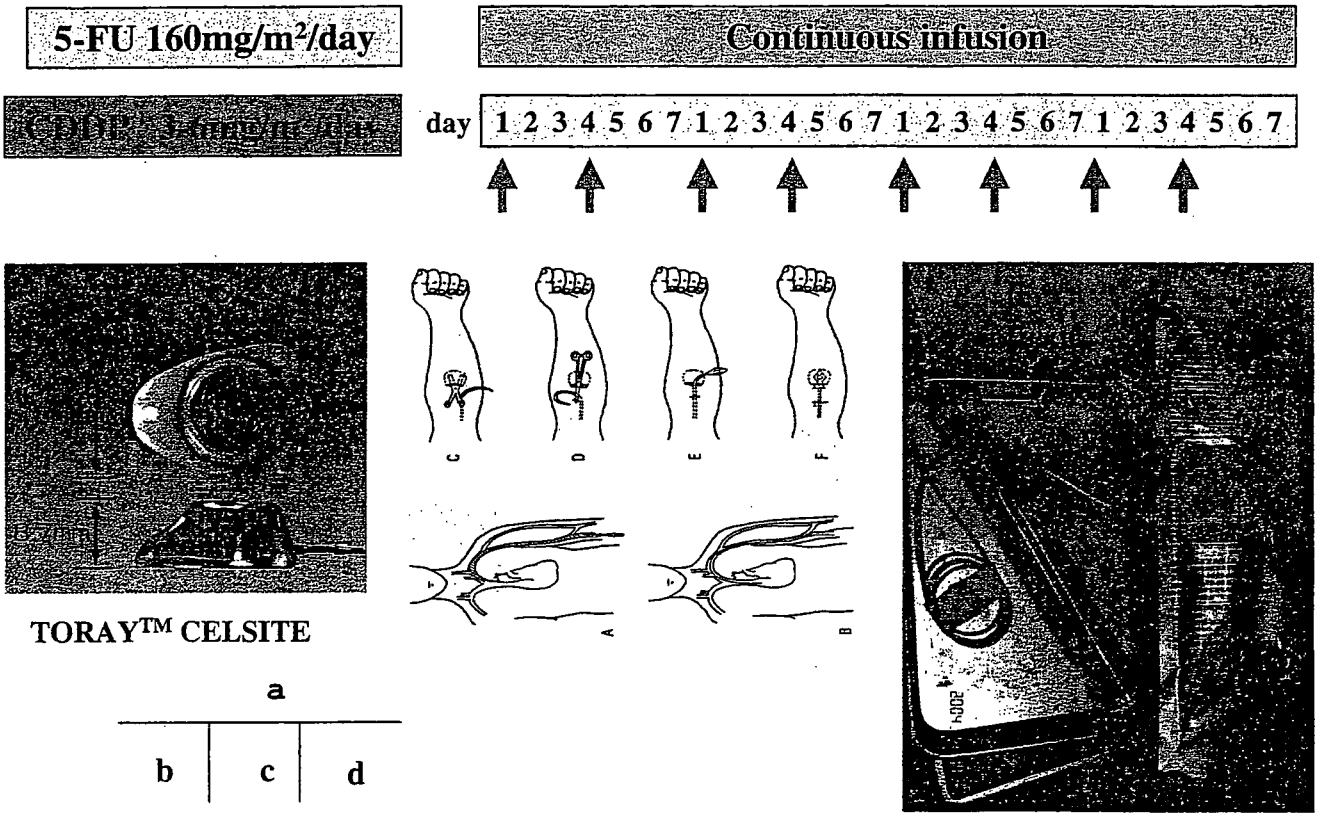


**Figure 1**

***Schedule for treatment and infusional method.*** A schematic drawing of the chemotherapy schedule (a), and the Central Venous catheter system consists of PAS port (b), implantation technique (c) and portable infusion pump (d).

**Figure 2.** *Survival and Treatment failure*

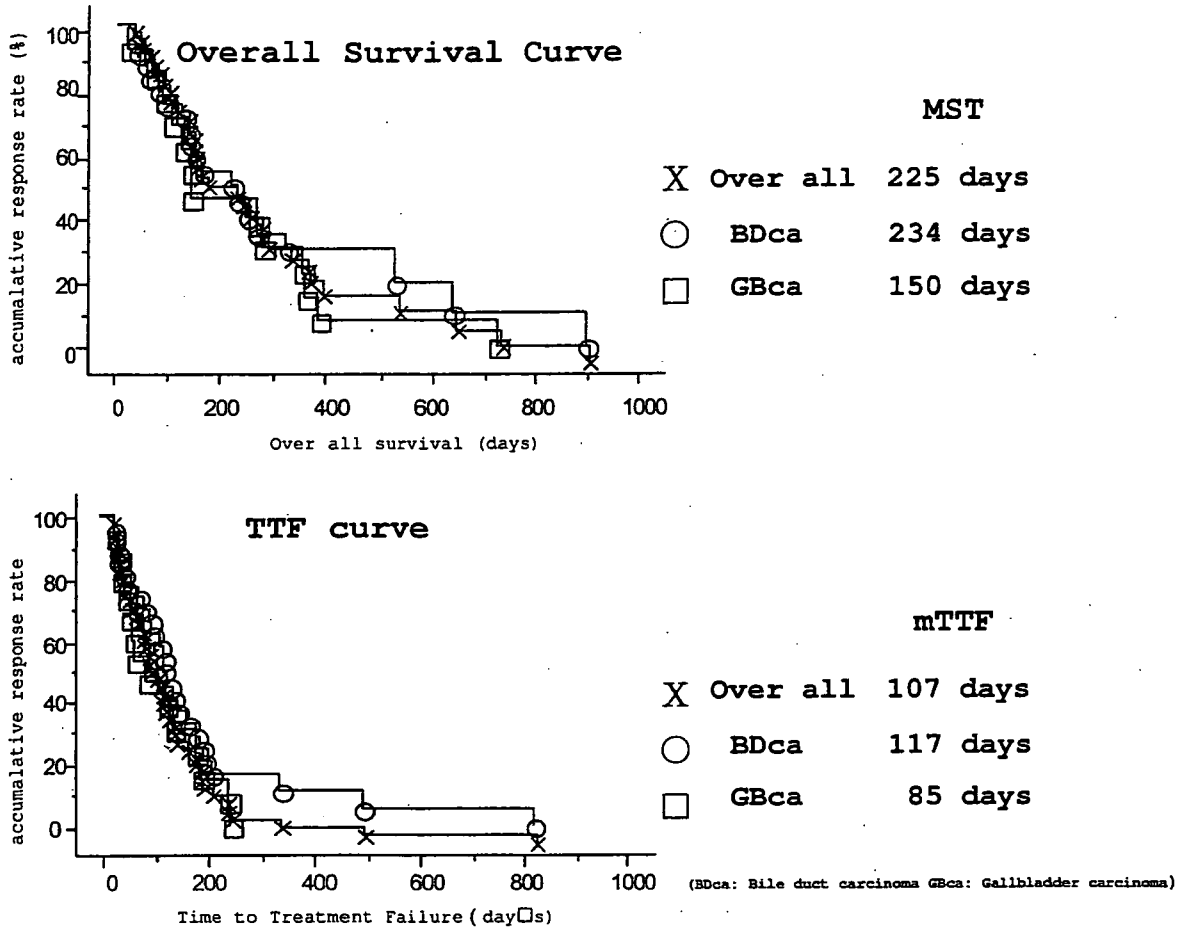


**Figure 2**
***Survival and Treatment failure.*** Kaplan-Meier curves of Overall Survival (upper column) and Time to treatment failure (TTF) (lower column) are shown.

month later. Target lesions were evaluated by a plain and enhanced CT scan and plain chest X-ray for each course.

### *Statistical analyses*

We used the Stat View J 5.0 software package (Abacus Concepts, Stat View. Abacus Concepts, Inc., Berkeley, CA, 1992–1998) for the statistical analysis. The time to Treatment Failure and the overall Survival Cumulative were obtained by the Kaplan-Meier method. The disease-free survival was compared by the Log rank test among the groups. Prognostic variables were evaluated by Cox's multivariate proportional hazard model. We defined the risk factors for LFP therapy for biliary tract malignancies in our study as significant factors based on both the Cox's and Kaplan-Meier's. A p value of less than 0.05 was considered to be statistically significant.

## Results

### *Patient characteristics*

From February 1996 to December 2003, 42 patients were enrolled into the present study, and all were evaluable for efficacy and toxicity analyses. They consisted of 24 males and 18 females. The mean age was 66.5(47–79). The number of patients with BDca and GBca were 27 and 15, respectively. Twenty-six patients who were initially diagnosed to have biliary tract malignancies were not eligible for surgery because of locally advanced disease and/or metastasis (locally advanced). Another 16 patients had local recurrence and/or distant metastasis after surgery (postoperative recurrence). Disease extension was such that 11 patients (BDca: 7, GBca: 4), had only primary or local recurrence patients had only metastatic disease (BDca: 9, GBca: 5), another 17 patients (BDca:11, GBca: 6) had both diseases. Four patients had previously undergone

**Table 1: Patient Characteristics**

| Variables | Startification | Over all | BDca | GBca |
|---|---|---|---|---|
| Spieces of cancer | | 42 | 27 | 15 |
| Sex | (male/female) | (24/18) | (17/10) | (7/8) |
| Age | | 66.5 ± 7.5 | 64.8 ± 8.2 | 69.5 ± 4.7 |
| ECOG PS | (0/1/2) | (36/4/2) | (22/4/1) | (14/0/1) |
| Disease Status | (unresectable/postoperative recurrence) | (26/16) | (15/12) | (11/4) |
| Disease extension | locally advanced (primary) | 26 | 15 | 11 |
| | local recurrence | 7 | 7 | 0 |
| | liver metastasis | 9 | 4 | 5 |
| | lung metastasis | 4 | 3 | 1 |
| | lymphnode metastasis | 11 | 4 | 7 |
| | miscellaneous metastasis | 5 | 5 | 0 |
| Tumor marker | carcinoembryonic antigen (CEA) | 16.7 ± 60.7 | 6.4 ± 17.2 | 36.7 ± 100.5 |
| | CA19-9 | 3035.5 ± 9507.6 | 4495.3 ± 11688.8 | 407.9 ± 587.2 |
| Previous chemotherapy | (yes/no) | (4/38) | (3/24) | (1/14) |

Abbreveations
BDca: bile duct carcinoma, GBca: Gallbladder carcinoma, ECOG PS: Eastern Cooperative Oncology Group performance status

chemotherapy, including such treatments as CDDP + VP-16, 5-FU + mitomycin C + farmorubicin, adriamycin + 5-FU. Two of 4 patients experienced surgery before these chemotherapy (i.e. postoperative recurrence). Seven of BDca patients had palliative radiotherapy. Three of these seven underwent surgery before radiation (i.e. postoperative recurrence). There were some differences between BDca and GBca on age, and serum tumor marker levels (CEA and CA19-9), but neither was statistically significant. The patient characteristics are enumerated in Table 1.

***Response and time-to-event measures***

The overall response rate (RR) was 42.9% (95% confidence interval C.I.: 27.7–59.0) with CR 0, PR 18, NC 13, PD 11, and clinical benefit was 73.8% (95% C.I.: 58.0–86.2). Patients with a PR, an NC or a PD required a confirmatory disease assessment at least two months later.

One GBca patient who got PR, could receive curative resection. The RR of primary lesion or locally advanced lesion was 50.0% (95% C.I.: 30.6–69.4), and the RR of

**Table 2: Anti tumor effect**

| | CR | PR | NC | PD | Response Rate (%)95%C.I. CR+PR/TOTAL | Clinical Response (%)95%C.I. CR+PR+NC/TOTAL |
|---|---|---|---|---|---|---|
| ***Over all*** | | | | | | |
| Over all | 0 | 18 | 13 | 11 | 42.9 (27.7–59.0) | 73.8 (58.0–86.2) |
| BDca | 0 | 11 | 10 | 6 | 40.7 (22.4–61.2) | 77.8 (57.8–91.4) |
| GBca | 0 | 7 | 3 | 5 | 46.7 (21.1–73.5) | 66.7 (38.4–88.2) |
| ***Primary or local recurrence*** | | | | | | |
| | CR | PR | NC | PD | Response Rate (%)95%C.I. CR+PR/TOTAL | Clinical Response (%)95%C.I. CR+PR+NC/TOTAL |
| Over all | 0 | 14 | 8 | 6 | 50.0 (30.6–69.4) | 78.6 (59.0–91.7) |
| BDca | 0 | 9 | 6 | 3 | 50.0 (26.0–74.0) | 83.3 (58.6–96.5) |
| GBca | 0 | 5 | 2 | 3 | 50.0 (18.6–81.4) | 70.0 (34.7–93.5) |
| ***Metastatic lesion*** | | | | | | |
| | CR | PR | NC | PD | Response Rate (%)95%C.I. CR+PR/TOTAL | Clinical Response (%)95%C.I. CR+PR+NC/TOTAL |
| Over all | 0 | 10 | 12 | 9 | 32.3 (16.7–51.4) | 71.0 (52.0–85.8) |
| BDca | 0 | 6 | 9 | 5 | 30.0 (11.8–54.3) | 75.0 (50.9–91.4) |
| GBca | 0 | 4 | 3 | 4 | 36.4 (10.8–69.3) | 66.7 (30.7–89.2) |

Abbreveations
BDca: bile duct carcinoma, GBca: Gallbladder carcinoma

**Table 3: Toxicity**

| Hematological Toxicity | Gr1 | Gr2 | Gr3 | Gr4 | ≧Gr3 (%) | Over all (%) |
|---|---|---|---|---|---|---|
| anemia | 0 | 11 | 0 | 0 | 0 (0) | 11 (26.2) |
| leukopenia | 0 | 1 | 0 | 0 | 1 (0) | 1 (2.3) |
| thrombocytopenia | 0 | 2 | 3 | 0 | 3 (7.1) | 5 (11.9) |
| **Non-hematological Toxicity** | **Gr1** | **Gr2** | **Gr3** | **Gr4** | **≧Gr3 (%)** | **Over all (%)** |
| nausea | 3 | 4 | 1 | 0 | 1 (2.3) | 8 (19.0) |
| vomiting | 1 | 1 | 3 | 0 | 1 (2.3) | 5 (11.9) |
| appetite loss | 0 | 0 | 6 | 0 | 6 (14.3) | 6 (14.3) |
| oral mucositis | 0 | 4 | 0 | 0 | 0 (0) | 4 (9.5) |
| taste disturbance | 0 | 1 | 0 | 0 | 1 (2.3) | 1 (2.3) |
| upper GI tract bleeding | 0 | 1 | 0 | 0 | 0 (0) | 1 (2.3) |
| diarrhea | 1 | 0 | 0 | 0 | 0 (0) | 1 (2.3) |
| general fatigue | 0 | 1 | 1 | 0 | 1 (2.3) | 2 (4.7) |
| jaundice | 0 | 0 | 4 | 0 | 4 (9.5) | 4 (9.5) |
| serum AST/ALT level elevation | 0 | 4 | 1 | 0 | 1 (2.3) | 1 (2.3) |
| Serum creatinine level elevation | 0 | 6 | 0 | 0 | 0 (0) | 6 (14.3) |

metastatic lesions was 32.3%. Various RRs were demonstrated in Table 2. The responses of meatastatic lesions were as such; liver (CR:0, PR:6, NC:0, PD:3), lung (CR:0, PR:1 NC:3, PD:0), lymph node (CR:0, PR:3, NC: 6, PD2), miscellaneous (CR:0, PR: 2, NC: 2, PD: 1). There was no significant difference in terms of anti tumor effects against both malignant neoplasms. The overall MST was 225 days. The median TTF was 107 days. Figure 2 Shows the BDca a longer MST and TTF than did GBca (234 vs 150, 117 vs 85, respectively), but neither difference was statistically significant.

### *Toxicity*

As shown in Table 3, neither any treatment related death nor grade 4 toxicity occurred. Overall, the most common toxicity was anemia occurring in 26.2% of patients followed by nausea (19.0%). The most frequent grade 3 toxicity was appetite loss (14.3%). The occurrence of ascites and jaundice may be partly because of the outcome of the disease progression.

### *Prognostic factors related survival and TTF*

An analysis of a Cox proportional hazard model showed that no significant factor was found prognostic factors for either the overall survival or TTF (Table 4). However, the patients with LFP courses ≧2 had both a longer overall survival and TTF than those with LFP courses < 2 as depicted in Figure 3. The distribution of the patients with LFP courses ≧2 was (PR/NC/PD = 16/8/3), while that of those with LFP courses ≤2 was (PR/NC/PD = 2/5/8).

**Table 4: Prognostic factors for over all survival and TTF**

| | Over all survival | | | Time to treatment Failure | | |
|---|---|---|---|---|---|---|
| Stratification | Hazard ratio | p-value | 95% C.I. | Hazard ratio | p-value | 95% C.I. |
| Sex (male/female) | 0.123 | 0.0128 | 0.024–0.640 | 0.225 | 0.0095 | 0.073–0.695 |
| Age (≧69/<69) | 0.634 | 0.6082 | 0.111–3.692 | 2.380 | 0.2269 | 0.583–9.713 |
| ECOG PS (PS0/PS1/PS2) | 0.016 | 0.0015 | 0.001–0.259 | 0.230 | 0.0007 | 0.001–0.152 |
| Species of tumor (BDca/GBca) | 0.095 | 0.0198 | 0.013–0.688 | 0.001 | 0.0411 | 0.0856–0.943 |
| Disease status (locally advanced/postoperative recurrence) | 0.121 | 0.0179 | 0.021–0.695 | 0.802 | 0.7388 | 0.001–0.152 |
| Radiation (yes/no) | 8.369 | 0.1491 | 0.467–150.112 | 0.603 | 0.4586 | 0.158–2.299 |
| Previous chemotherapy (yes/no) | 0.143 | 0.0255 | 0.016–1.241 | 0.495 | 0.4086 | 0.094–2.622 |
| Initial CEA level (≧1 UL/<1 UL) | 1.098 | 0.9053 | 0.234–5.160 | 2.453 | 0.1267 | 0.775–7.763 |
| Interval decreasing CEA level (yes/no) | 0.224 | 0.2859 | 0.014–3.499 | 1.734 | 0.5968 | 0.260–11.568 |
| Initial CA19-9 level (≧5 UL/<5 UL) | 0.078 | 0.0255 | 0.014–3.499 | 1.734 | 0.5968 | 0.260–11.568 |
| Interval decreasing CA19-9 level(yes/no) | 1.449 | 0.7667 | 0.125–16.774 | 0.326 | 0.2600 | 0.047–2.290 |

(Cox proportional hazard model)

Abbreveations

BDca: bile duct carcinoma, GBca: Gallbladder carcinoma, ECOG PS: Eastern Cooperative Oncology Group performance status, CEA: carcinoembryonic antigen, UL: upper limit

Figure 3. *Relation between number of LFP courses and Over all survival and TTF*

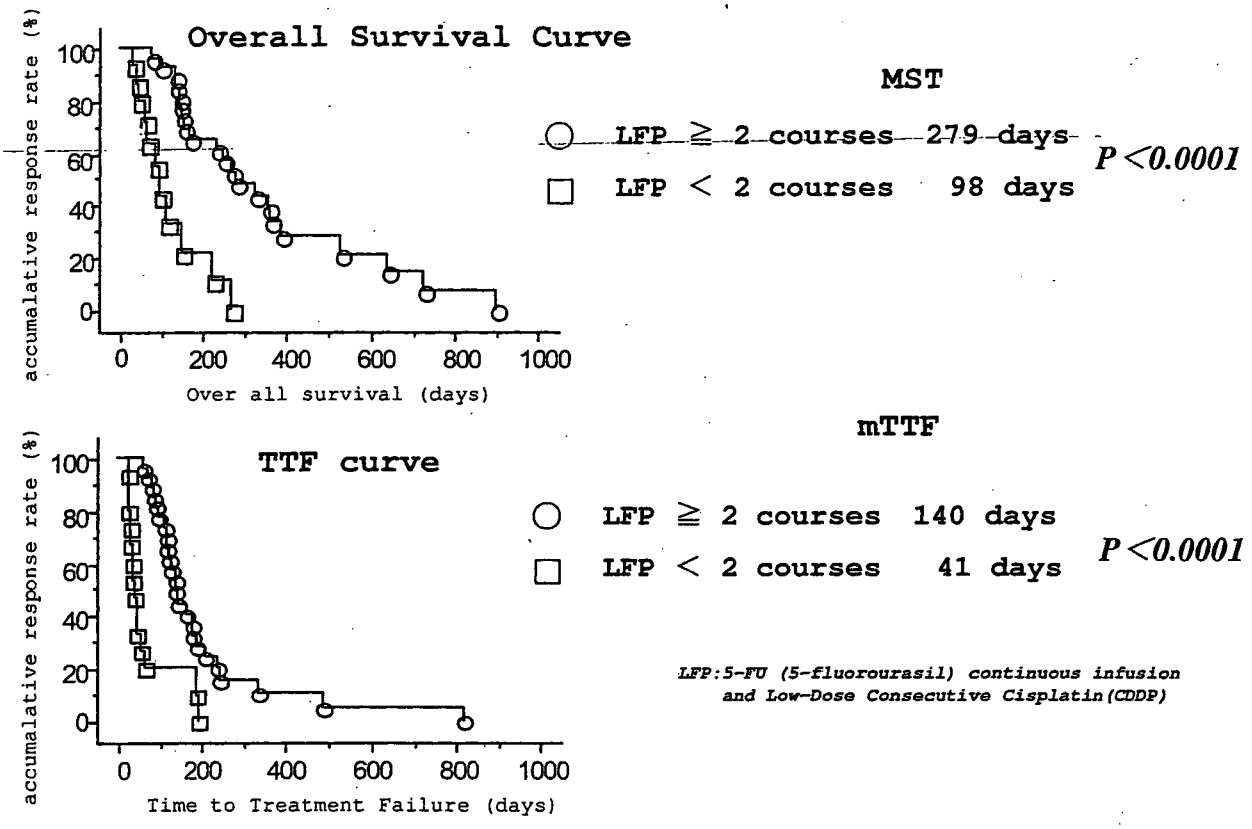


**Figure 3**

***Relation between number of LFP courses and Over all survival and TTF.*** Differences by accomplished LFP (5-FU (5-fluorourasil) continuous infusion and Low-Dose Consecutive Cisplatin(CDDP)) courses are depicted regarding the overall Survival (upper column) and Time to treatment failure (TTF)(lower column).

### *Cost benefit*

The difference between the inpatient-basis and the outpatient-basis or home treatment of this therapy in respect to cost is shown in Table 5. This was calculated based on the assumption that one patient received one-month treatment of this LFP therapy covered by Japanese National Health Insurance. The cost for outpatient-basis/home LFP therapy was approximately equivalent to 996 U.S. dollars which was about one-sixth less than the cost on an inpatient-basis.

## Discussion

In the present study, we achieved an RR of 42.9% (95% C.I.: 27.7–59.0) with a median over all survival of 225 days and median TTF of 107 days. No grade 4 toxicity or treatment related death occurred. The cause of treatment failure of the other 37 patients was an aggravation of general condition due to primary disease, and not due to any adverse effect. LFP therapy showed a good compliance and the adverse effects were either tolerable or controllable.

The overall response rate of our study is relatively high for this type of tumor. However, our LFP method has achieved more than a 50% overall response rate in other tumors such as esophageal, gastric or colon cancers. Biliary tract cancer may be more malignant than other types of cancer.

One cycle of conventional LFP therapy consists of CDDP infusion consecutive five days per week and 24 hr continuous infusion of 5-FU consecutively 7 days per week [14].

**Table 5: Cost-benefit**

| Outpatient-basis or home | Inpatient-basis |
|---|---|
| At home malignant tumor | Basic admission fee 472,900 yen |
| Administration fee 25,000 yen | Local infusion technical fee (addition to minute infusion) 46,200 yen |
| Portable infuser pump | |
| using fee 15,000 yen | Diet 63,600 yen |
| Medication | Medication |
| CDDP 20,000 yen | CDDP 20,000 yen |
| 5-FU 15,000 yen | 5-FU 15,000 yen |
| Tumor marker 5,000 yen | Tumor marker 5,000 yen |
| Other laboratory test 8,400 yen | Other laboratory test 8,400 yen |
| Imaging diagnosis 15,000 yen | Imaging diagnosis 15,000 yen |
| (antiemeric drug 16,000 yen) | (antiemeric drug 16,000 yen) |
| Total 103,600 (119,600) yen | Total 646,300 (662,300) yen |

(One month treatment covered by Japanese National Health Insurance, A U.S. dollar is approximately equivalent to 104 Japanese yen)

Therefore, the patients were obliged to receive inpatient-basis treatment, which led to their inconvenience and a heavy burden due to the high admission fee. Regarding the five consecutive days of CDDP infusion, our preliminary study showed that CDDP infusion twice a week was sufficient to maintain the blood concentration of CDDP in order to achieve synergistic effect [15]. This fact and the application of a CV catheter system with PAS or vital port and portable infusion pump thus enable the patients to receive outpatient-basis treatment which is equivalent to the inpatient treatment in quality. As for central venous catheter, Knox reported six catheter infection cases occurred in 27 patients [6], but no complications related to the catheter system occurred in our study. Our good results were due to the easy technique of implantation associated with the catheter system [19]. In our hospital from July 1994 to December 2002, infection related to the CV-catheter system occurred in only 44 cases of total 1,350 implanted patients (3.4%).

We herein tried to compare our regimen with other combination chemotherapies [2,4-6,21-23] are summarized in Table 6. Our combination chemotherapy is thus considered to be effective enough to be recommended the biliary tract malignancy since our study achieved a low toxicity and high efficacy with a relatively higher RR and longer MST in comparison to these regimens. Kim's regimen [4] is also interesting since oral capesitabine was used. However, our results showed higher response rate and lower toxicity than Kim's.

**Table 6: Current Combination Chemotherapy for Biliary tract cancer**

| Author (published year) | Number of Patients | Species of cancer | Regimen | RR (%) | MST (days) | mTTF (days) | Adverse effects (≧Gr3) | Treatment related death |
|---|---|---|---|---|---|---|---|---|
| Ishii(2004) | 21 | GBca | CEF(CDDP/5-FU/ epirubicin) | 33.3 | 177* | - | hematological toxicity (52.3%) | none |
| | 25 | GBca | FAM(5-FU/Doxorubicin/ Mitomycin) | 7.1 | | - | hematological toxicity (20%) | none |
| Lee (2004) | 4 | BDca | Gemsitabine/CDDP | 50 | 270 | 150 | thrombocytopenia (75%) | none |
| Doval(2004) | 30 | GBca | Gemsitabine/CDDP | 36.6 | 140 | 126 | nausea/vomiting (16%) | 2 |
| Malik(2003) | 11 | GBca | Gemsitabine/CDDP | 64 | 294 | 196 | anemia (45%) | none |
| Knox (2004) | 27 | BDca/ CBca | Gemsitabine/5-FU | 33 | 159 | 111 | hematological toxicity (11%) | none |
| Malik(2003) | 30 | CBca | Leucovorin/5-FU | 7.5 | 444 | 141 | diarrhea (30%) | 1 |
| Kim (2003) | 42 | BDca/ CBca | Capesitabine/CDDP | 21.4 | 273 | 111 | leucopenia (20%) | none |

(* The result was overall survival of combined CEF and FAM)
Abbreveations
BDca: bile duct carcinoma, GBca: Gallbladder carcinoma, CDDP: Cisplatin, 5-FU: 5-fluorourasil, RR: response rate, MST: median survival time, mTTF: median time to treatment failure

One of the problems of our study was that the prognosis of the patients receiving less than two courses of LFP was remarkably poor as shown in Figure 3. Of these patients only one could receive second-line chemotherapy with CDDP/CPT-11. It is important to predict whether LFP therapy is effective or not. Fortunately, an effective method for predicting LFP therapy effectiveness for gastrointestinal cancers by detecting p53 has been reported [16-18]. This method may be applicable for biliary tract malignancy.

The present study used 5-FU continuous venous infusion (CVI) as an effector. If an oral drug which can help maintain a high blood concentration of 5-FU equivalent to or higher than that for the CVI-method exist, then the patients with biliary tract malignancy can avoid the need to use the catheter system but while still achieving an improved anti-tumor effect thus leading to an advanced quality of life. S-1 invented by one of the authors (T.S) [11] can thus be one of the candidates for this aim. S-1 is a novel oral fluoropyrimidine that consists of tegafur, which is a prodrug of 5-FU, 5-chloro-2, 4-dihydroxypyrimidine, which inhibits dihydropyrimidine dehydrogenase activity and potassium oxonate, which reduces gastrointestinal toxicity [11,24]. This feature helps to maintain a high blood concentration of 5-FU and less toxicity of digestive tract [11,24]. The result of 101 advanced gastric cancer patients with S-1 was reported to be 44.6% RR with 244 days of MST [25,26]. Furthermore, using the synergistic effect of LFP, the combination chemotherapy of CDDP and S-1 has also been performed for gastric cancer or pancreatic cancer at some institutes [13,25,27-30]. Many reports have so far described promising results. The application of low-dose CDDP and S-1 for biliary malignancies at our institute is now under consideration. Our study of LFP is thus considered to support the use of low-dose CDDP and S-1 regimen for BDca and GBca.

## Conclusion

In conclusion, this outpatient-basis LFP therapy is considered to be appropriate as a first-line treatment for either advanced or recurrent biliary tract cancer and it promises to help improve the quality of life of cancer patients while also facilitating the clinical management of such patients.

## Competing interests

The authors declares that they have no competing interests.

## Authors' contributions

KK carried out this study, and drafted this manuscript. AT conceived the design of present study. SM participated in assessing radiological findings. TH participated in its design and coordination. TS participated in the pharmacological basis of the study. TK participated in the coordination of this study and instructed the collaborators of this manuscript.

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# 消化器がんの化学療法

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## 化学療法の役割

化学療法とは，全身のがん細胞を治療することのできる可能性を持つ治療の一つである。ほとんどの場合，がん細胞は正常細胞より早い周期で分裂し，化学療法は，この細胞が最も傷害を受けやすいこの時期に作用することにより抗腫瘍効果を示す。

ところが，分裂周期の早い正常細胞（粘膜・髪の毛・骨髄など）も存在するため，このような組織では抗がん剤の副作用を受けやすいということになる。よって実際の治療では，ある薬剤の効果を高める薬剤を数種類併用したり，投与時間を調節したり，また，がん細胞の分裂周期の特定の時期に効果を持つ薬剤を併用したりすることにより，副作用を最小限に抑えるような工夫を行っている。

近年では，新規抗がん剤の開発や，種々の抗がん剤（5-FUなど）に対する各種薬剤の作用増強効果が解明されたことなどにより，化学療法の効果も高まり，さらにその適応疾患は広がりつつあり，今後が期待されている。

## 消化器がんの化学療法

消化器がんの化学療法は，白血病などの高い感受性を持つ腫瘍に比べれば，十分な効果があるとは言えない。従来は，高い感受性を持つ腫瘍と同様の考え方で治療が行われ，少しでも多い量の抗がん剤を使用し，それを補助する支持療法を強力に行って効果を高める努力をしてきた。また，新規抗がん剤や新たな投与方法（5-FUの１回投与を上回る効果を示す持続投与法の解明など）[1]により，治療成績の向上が得られている。

さらに，治療に対する概念の変革も進んできている。具体的には，腫瘍が増大していく時間の比較的遅い消化器がんにおいては，化学療法の副作用の出現を抑えながら，繰り返しかつ頻回に治療を行い継続することで，生存期間の延長と腫瘍縮小効果の増強を得る，といった考え方である。

## 各種消化器がんの主な化学療法

### 1）食道がん

食道がんの治療において化学療法の主要な役割は切除不能進行食道がんに対するものである。欧米をはじめとして術前補助化学療法としての治療も行われているが，その明らかな生存期間に対する効果はまだ証明されていない。

食道がんに対し，単剤では生存期間に対する有用性は認められず，化学療法の効果が少ないとされていた

が，CDDPの導入以来本剤を中心とした併用療法により治療効果の改善が得られている。現在ではCDDP＋5-FU（FP）療法が奏効率と副作用の点で優れた成績を示し，標準療法[2]の地位を得ている。

また，近年はDocetaxel（DTX），paclitaxel（PTX），nedaplatin（254-S），vinorelbine（VNB），irinotecan（CPT-11）などの薬剤の効果が注目されており，単剤および併用での検討が注目される。

放射線併用療法については本稿では詳細は述べないが，現在では放射線単独療法をしのぐ効果があるため，今後手術療法に変わって標準的治療となることが期待されている。

**【代表的な治療法】**

①CDDP＋5-FU（FP）療法（図1）

投与方法

| |
|---|
| CDDP　80（～100）mg/m²/day |
| day 1　点滴静注（div） |
| 〈またはCDDP　20mg/m²/day |
| day 1～5　点滴静注（div）〉 |
| 5-FU　800（～1,000）mg/m²/day |
| day 1～5　持続静注（CVI） |

主な毒性

血液毒性（白血球・顆粒球減少，血小板減少，貧血），腎毒性，消化器毒性（悪心・嘔吐，下痢，口内炎，食道炎），精神神経毒性（錐体外路症状，意識障害，運動障害，言語障害），その他

注意点

腎障害や消化器毒性，血液毒性の出現頻度は高いため，注意が必要である。特にCDDPは腎排泄であるので腎障害の予防のため尿量のチェック，必要に応じて点滴の追加が必要

CDDP 80（～100）mg/m²/day 1

↓

5-FU ci 800（～1,000）mg/m²/day1～5

d1　　d5

every 28 days

投与スケジュール day1，2，3，4，5/28

| 投与順 | 投与薬剤 | 投与量 | 投与法 |
|---|---|---|---|
| day1 | 1　ナゼア注0.3mg　2mℓ | 0.3mg | ワンショット静脈注射 |
| | ブドウ糖注5%　20mℓ | 20mℓ | |
| | 2　デカドロン注　8mg　2mℓ | 12mg | 点滴静注　0.5時間 |
| | 生理食塩水　100mℓ | 100mℓ | |
| | 3　ランダ注　50mg　100mℓ | 80（～100）mg/m² | 点滴静注　2時間 |
| | 生理食塩水　1ℓ | 1,000mℓ | 遮光 |
| | 4　マンニトール注20%　300mℓ | 300mℓ | 点滴静注　2時間 |
| | 5　5-FU注250mg　5mℓ | 800（～1,000）mg/m² | 中心静脈（埋め込み型カテーテル） |
| | 注射用水20mℓ | 5-FUと合計45mℓ | バクスター　シングルデイインフューザー使用 22時間 |
| day2 | 1　ナゼア注0.3mg　2mℓ | 0.3mg | ワンショット静脈注射 |
| | ブドウ糖注5%　20mℓ | 20mℓ | |
| | 2　デカドロン注　8mg　2mℓ | 12mg | 点滴静注　0.5時間 |
| | 生理食塩水　100mℓ | 100mℓ | |
| | 3　5-FU注250mg　5mℓ | 750mg/m² | 中心静脈（埋め込み型カテーテル） |
| | 注射用水20mℓ | 5-FUと合計49mℓ | バクスター　シングルデイインフューザー使用 24時間 |
| day3,4,5 | 1　5-FU注250mg　5mℓ | 750mg/m² | 中心静脈（埋め込み型カテーテル） |
| | 注射用水20mℓ | 5-FUと合計49mℓ | バクスター　シングルデイインフューザー使用 24時間 |

**注意すべき有害事象**　腎毒性，血液毒性，消化器毒性

**注意点**　day 1，2の1，2は有害事象に対する前投薬（推奨）
在宅化学療法加算 1,500点＋携帯型ポンプ加算 2,500点算定可
CDDPはClイオン存在下でないと不安定となるので生理食塩水で希釈。アミノ酸製剤などと混注しないこと
CDDP投与中は他の薬剤を一時休止が望ましい
終了後自己抜針
day1：インフューザー総量45mℓ＝2mℓ/h×22時間（44mℓ）＋ポンプに残る量（1 mℓ）
day2～5：インフューザー総量49mℓ＝2mℓ/h×24時間（48mℓ）＋ポンプに残る量（1 mℓ）

**図1 FP療法**

となる。この際，CDDPが不安定な白金錯体であり，配合禁忌も多いことに留意し，できるだけ生理食塩水などを用いることが望ましい（アミノ酸製剤などは避けることが望ましい）。

白血球・顆粒球減少に対してはG-CSFの使用も認められている。

消化器毒性のうち悪心・嘔吐に関しては，症状発現の兆しが治療の良いタイミングである。いったん出現すると完全には抑えることが困難となるため，速やかに制吐剤（5-HT$_3$拮抗剤など）の投与を行うことがポイントである。

口内炎も多く見られる。口腔内を清浄に保ち予防することが基本であるが，出現した際は早期治療が望ましい。

②low-dose FP療法

| |
|---|
| CDDP　3 mg/m$^2$/day　day 1～5 点滴静注30分（4週投薬1週休薬） |
| 5-FU　170mg/m$^2$/day　day 1～7 7日間持続静注（4週投薬1週休薬） |
| 〈または5-FU　250mg/m$^2$/day day 1～5　持続静注（5日投薬2日休薬　毎週）〉 |
| 可能な限り繰り返す |

60％前後の高い奏効率[4]が報告されている。

副作用はほかの治療法と比較し軽微である。grade 3以上の副作用発現率は数％と低い。また多くは軽度の悪心・嘔吐であり，初回治療時の対応で副作用が回避可能であることも多く，制吐剤（必要に応じ5-HT$_3$拮抗剤など）の使用が肝要である。

FPとlow doseFP療法との放射線併用での比較試験が食道がんで行われている。

③DTX療法

胃がんの項を参照のこと。

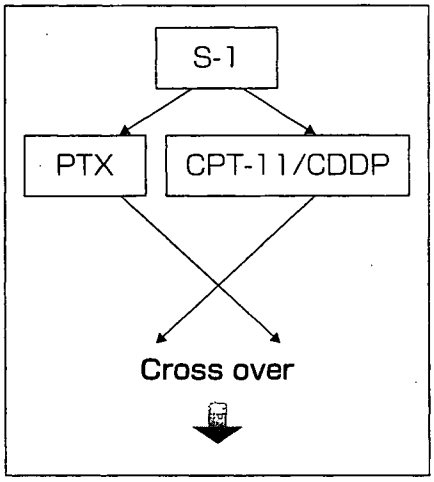
④DCF療法

胃がんの項を参照のこと。

## 2）胃がん

2006年12月も術後補助化学療法としてのTS-1療法の有用性が報告され，今後標準的補助化学療法となると考えられる。進行・再発胃がんに対しては，1992（平成4）年以降，化学療法の有用性が示されるようになってきた。さらに近年開発されたCPT-11やTS-1などの薬剤による治療成績の向上はめざましいものがあり，一部のphase Ⅱ試験などでは70～80％という極めて高い奏効率が報告され始めており，今後が期待されている。

現在は次の図のようなTxが選ばれていることが多い。現在Second line以降については臨床試験が進んでいる。




【代表的な治療法】

①5-FU持続静注療法

| |
|---|
| 5-FU　800mg/m$^2$　持続静注 day 1～5　28日ごと（可能な限り繰り返す） |

副作用は消化器毒性（悪心・嘔吐，下痢，口内炎，皮膚炎）が多く，ほかに血液毒性（白血球・顆粒球減少，血小板減少，貧血）も認められる。また精神神経毒性（錐体外路症状，意識障害，運動障害，言語障害）も認められるが，中でも重篤なものとしては白質脳症があり（比較的長期間の治療の後出現することが多い）注意が必要である。

従来は胃がんにおける標準的治療[3]であった。最近では他療法の成績向上によりその位置づけは2007（平成19）年にも大きく変わる可能性がある。

②low-dose FP療法

食道がんの項を参照のこと。

③FP療法

食道がんの項を参照のこと。

④MTX＋5-FU療法[5]

| |
|---|
| MTX100mg/m$^2$　one shot静注 day 1 |
| 5-FU　600mg/m$^2$をone shot静注 day 1（MTXの3時間後） |
| ロイコボリン　45mg　3×6時間ごと（MTX投与24時間後より2日間経口投与） |

維持輸液下に尿のアルカリ化を図るためにメイロン40mℓ，ダイアモックス250mgを混注する。尿が酸性化するとMTXの結晶が尿細管に詰まるため，尿を酸性化する利尿剤（ラシックスなど）を使用しない。プロスタグランジンE 2の合成阻害のため，腎血流の低下によるMTXの毒性増強を防ぐため非ステロイド系消炎鎮痛剤（ボルタレンなど）の使用を避ける。

以上を1ないし2週ごと施行。副作用回避のため，血中MTX濃度モニターが有用である。

副作用としては下痢，白血球減少，口内炎など。特に下痢は難治性のことが多く厳重な注意が必要である。

初回治療例の奏効率は20～50%とされている。

⑤CPT-11＋CDDP療法[6]

| |
|---|
| CPT-11　70mg/m²　点滴静注 day 1，15<br>CDDP　60mg/m²　点滴静注 day 1　（4週ごと） |

第2相試験では50%近い奏効率が認められた。

骨髄抑制（特に白血球減少，血小板減少），全身倦怠感，悪心・嘔吐，下痢などの副作用が比較的高頻度に認められる。

⑥LV＋5-FU療法

大腸がんの項を参照のこと。

⑦S-1療法（TS-1）[7]

| |
|---|
| 体表面積<br>1.25m²未満：80mg/day，<br>1.25m²以上1.50m²未満：100mg/day，<br>1.50m²以上：120mg/day<br>1日2回，28日間連日投与，14日間休薬 |

単剤で40～50%の高い奏効率が認められた。

また骨髄抑制（特に白血球減少，血小板減少），全身倦怠感，悪心・嘔吐，下痢，皮膚症状，色素沈着，発熱などの副作用も高頻度（70～80%）に認められる。

有効性も副作用も高く従来の経口抗がん剤とは一線を画す薬剤であり，慎重に適応を検討する必要がある。

⑧Paclitaxel療法[8]

3週毎投与方法

| |
|---|
| Paclitaxel　210mg/m²，3時間点滴，（3週ごと） |

第2相試験において，奏効率は23.4%，前化学療法を有する症例でも22.7%であった。また，生存期間中央値が単剤で303日と生存に寄与する可能性も示唆されている。

副作用は脱毛や骨髄抑制（特に顆粒球減少）が認められ，溶解剤によるアレルギー反応を防ぐために十分な前処置が必要である。また末梢神経障害，皮疹も注意が必要である。

放射線治療，CDDP，ADRの併用には相互作用があるので慎重投与が必要である。

Weekly投与法

| |
|---|
| Paclitaxel　80mg/m²/day 1，8，15；1時間点滴，4週ごと |

卵巣がんなどで有効性が示され，現時点ではこちらが主流となり，今後さらに増えてくることが予想される。

前投薬

Paclitaxel投与による過敏症予防のため，以下の前投薬を行う（Paclitaxel投与30分前までにすべて完了）。

| |
|---|
| デカドロン　24mg　iv<br>ポララミン5　mg　iv（またはベナ50mg　内服）<br>ザンタック　50mg（またはガスター20mg）iv |

⑨DTX療法[9]

| |
|---|
| Docetaxel　60mg/m²/day 1を専用溶解液（13%アルコール）に溶解後生理食塩水（または5%ブドウ糖溶液）500mℓに加え，1～2時間で点滴静注（3週ごと）。 |

奏効率は20～30%。

副作用は脱毛（約80%，完全脱毛約20%），骨髄抑制（特に顆粒球減少），末梢神経障害（約10%）が挙げられる。また浮腫（約6%）や体腔液貯溜は本剤に特徴的なものである。

浮腫に対しては利尿剤（ラシックス，アルダクトンなど）の使用やステロイドの予防投与（デカドロンなど）が行われる。DocetaxelにおいてもPaclitaxelほどではないがアレルギー反応の出現を認める。

⑩DCF療法

DCFvsCF（FP）との比較試験でCF療法をしのぐ成績が得られ，アメリカでFirst lineとして勧められている（表1）。

### 3）肝臓がん

化学療法の感受性は低く標準治療とされるものはないが，近年いくつかの臨床試験で有用性を示す結果が報告[14]されている。

**【代表的な治療法】**

①low-dose FP療法

胃がんの項を参照のこと。

40～60%の高い奏効率が報告されているが，CDDPは保険適応がなく，現在臨床試験が行われている。

②low-dose FP動注療法

| |
|---|
| CDDP　7mg/m²/day　day 1～5<br>1時間肝動注<br>5-FU　170mg/m²/day　day 1～5<br>CDDP投与後5時間肝動注 |

全身投与と同様に，60%以上の高い奏効率も報告されている。