再切除の結果は良好である[53),64)].

III. リンパ節転移の外科治療

1986～1998年の初回手術時および再発で診断された遠隔リンパ節転移部位を**表4**に示した．初回手術例では62例中38例61％が他臓器転移との合併であり，そのような症例ではリンパ節転移も複数部位に及んでいることも多くて外科的切除の対象とならない．小腸間膜リンパ節転移は初回手術時に発見されて原発巣とともに切除されたものである．Virchow転移や縦隔リンパ節転移は切除対象とならない．

1. 大動脈リンパ節転移

初回手術時13例と再発1例に切除が行われた(**表5**)．生存期間中央値は2年(6カ月～12年)で無再発生存は1例(12年生存中)のみである．非切除10例(再発4，初回手術時6)の生存期間中央値4.5カ月(3カ月～2年4カ月)と比べて郭清例のほうが長期生存しているが，決して予後が良いとはいえない．初回手術13例の大動脈リンパ節転移は11例で複数個の転移があった(1～12個)．無再発生存例は3個の転移があった．したがって郭清は転移疑いのリンパ節をつまみ取りするのではなく，左腎静脈より尾側の大動脈リンパ節の完全郭清が必要である．術後の再発は14例中8例で遠隔リンパ節が初再発部位だった．大動脈リンパ節転移のある症例では総リンパ節転移個数も平均17個(10～52個)と多く，単に大動脈に転移があることのみでなく，総リンパ節転移個数が多いことも予後不良の理由と思われる．

表4　大腸癌遠隔リンパ節転移の状況

	初回手術時		再発
	遠隔リンパ節転移のみ	他臓器転移との合併	
大動脈リンパ節			
郭清	13		1
非郭清	6	25	5
鼠径リンパ節			
郭清	4		1
非郭清		1	3
小腸間膜			
郭清	1	3	
後腹膜リンパ節			
非郭清			1
Virchow			
非郭清		4	1
縦隔リンパ節			
非郭清			1
骨盤内リンパ節(直腸癌を除く)			
非郭清		5	

2. 鼠径リンパ節転移

初回手術4例と再発1例に郭清あるいは転移巣切除が行われた(**表6**)．生存期間中央値は3年1カ月(3カ月～8年)で，非切除3例の1年0カ月(10カ月～1年10カ月)よりも良好であるが，5年以上生存は1例のみだった．肛門の扁平上皮癌は原発巣に対しては放射線療法あるいは化学放射線療法が第一選択となっている．症例②は鼠径リンパ節転移に照射を行ったが完全緩解(CR)が得られず，その後に鼠径リンパ節郭清を行った．鼠径部の創が照射のために治癒せず，感染を起こして大腿動脈が破綻して出血死した．それ以後，扁平上皮癌の鼠径リンパ節転移に対しては郭清を行って，創が治癒した後に照射を追加している．腺癌の鼠径リンパ節転移例に5年生存例はなかった．

3. 直腸癌術後の骨盤内リンパ節再発

直腸癌術後の骨盤内リンパ節再発は局所再発の一形式として扱われている．再発リンパ節は内腸骨，閉鎖の側方リンパ節あるいは総腸骨リンパ節の再発であるが，いずれも骨盤壁に浸潤あるいは近接していて完全切除が行いにくく，また再発が多い．

表5　大動脈リンパ節転移切除例

症例	組織型	大動脈リンパ節転移個数	総リンパ節転移個数	生存期間	予後	初再発形式	補助療法
初回手術例							
① Rb	中分化	12	26	2年 4月	癌死	肺	化療
② Rs	中分化	7	12	2年 8月	癌死	肝	化療
③ S	中分化	3	10	2年10月	癌死	大動脈リンパ節	化療
④ Rab	低分化	2	21	6月	癌死	局所	なし
⑤ Ras	中分化	5	15	2年 5月	癌死	腹膜	なし
⑥ Rb	中分化	8	18	8月	癌死	鼠径リンパ節	化療
⑦ Rs	中分化	3	10	12年	生	なし	化療
⑧ S	中分化	11	17	3年 0月	癌死	Virchow	化療
⑨ Rba	粘液	1	16	3年 1月	癌死	大動脈リンパ節	化療
⑩ C	中分化	3	52	1年 1月	癌死	大動脈リンパ節	化療
⑪ Ra	粘液	1	15	1年 1月	癌死	腹膜	照射
⑫ Rsa	中分化	4	29	9月	癌死	Virchow	化療
⑬ Ra	中分化	5	36	10月	癌死	Virchow	なし
再発例							
⑭ Ra	中分化			1年 8月	癌死	縦隔リンパ節	

表6　鼠径リンパ節転移切除例

症例	組織型	原発巣治療	鼠径転移治療	生存期間	予後	初再発形式
初回手術例						
① P	粘液	APR＋化療	郭清	3年 1月	癌死	反対側鼠径リンパ節
② P	扁平上皮癌	照射＋化療	照射＋郭清	3月	他病死	
③ P	扁平上皮癌	局所切除＋照射	郭清＋照射	8年	生	なし
④ Rb	中分化	APR＋照射	転移巣切除	2年 4月	癌死	肺
再発例						
⑤ Rb	中分化	APR	郭清＋照射＋化療	3年 9月	癌死	肺

APR：腹会陰式直腸切断術

おわりに

大腸癌の肝転移と肺転移に対する治療の第一選択は完全切除であることはconsensusが得られている．これはカスケード理論によって，転移巣が全身散布される前に肝あるいは肺に転移巣が限局している間に切除して治癒を目指そうとするものであり，現在のテーマはどのような症例に切除の適応があるかの術前の見定めである．厚生労働省の研究班では，肝，肺転移に対して切除のためのstage分類あるいは予後予測モデルを作成した[60),65)]．

一方，遠隔リンパ節転移は発見された時点ですでに全身に癌は散布されているものと考えなくてはならず，明確に外科適応を定めることはできない．文献的にも，遠隔リンパ節の外科治療について少数例での検討はあっても治療方針を述べた報告はない．今回の検討では切除例に治癒が期待できる例があることは推測できたが，多数症例での検討が必要である．

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Summary

Surgery for colorectal liver, pulmonary and lymph node metastases

Tomoyuki Kato*, Takashi Hirai*
and Yukihide Kanemitsu*

The prognosis for patients with metastases from colorectal cancer that remain unresected is poor and complete resection of metastases is the only known treatment associated with long-term survival.

For hepatic metastases there are two types of hepatic resection ; anatomic resection and wedge resection. The five-year survival rate after hepatectomies is 20 ~50%. Repeated hepatectomies and regional lymphadenectomies may be effective in prolonging the survival of selected patients with hepatic metastases. The following factors were found to be predictors of poor long-term outcome : positive margins, regional lymph nodes which were positive, satellite nodules and invasive factors, extrahepatic disease, a large number of hepatic tumors, postoperative CEA level>5ng/m*l* and postoperative CA19-9 levels>50ng/m*l*.

For pulmonary metastases there are the following types of treatments ; wedge resection, lobectomy and pneumonectomy. The use of video assisted thoracic surgery (VATS) in the management of pulmonary metastases is being evaluated. The five-year survival rate is 16~62 %.

The important prognostic factors are follows: incomplete resection, hilar and mediastinal lymph node metastases, histology of the primary site, high preoperative CEA levels, and disease free interval from time of colectomy to pulmonary metastatectomy.

Concerning lymph node metastases: In patients with para-aortic lymph node metastases, the median survival time was 24 months in patients receiving lymph node dissection and 4.5 months without lymph node dissection. In those with inguinal lymph node metastases, the median survival time was 37 months with lymph node dissection and 12 months without lymph node dissection.

**Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan*

Key words : metastases from colorectal cancer, hepatic metastases, pulmonary metastases, lymph node metastases, surgery for metastases from colorectal cancer

3. 大腸癌肝・肺転移に対する切除*

高橋進一郎　木下　平　永井完治　斉藤典男**

〔要旨〕進行大腸癌では，肝転移単独，肺転移単独だけでなく，肝転移，肺転移を同時にもしくは引き続き認める肝・肺転移を比較的多く認める．現在，これらの症例には全身化学療法を中心とした治療が行われているが，今回，手術可能例に積極的に外科的切除を行った成績を検討したところ，5年生存率11～54%と比較的良好な成績であった．外科的切除は，大腸癌肝・肺転移例に対する有効なオプションと考えられる．

はじめに

進行大腸癌に対し根治切除を行った症例の約40%に再発が認められる．とくに，肝転移(33%)，肺転移(22%)は高頻度であり[1]，治療成績向上の大きな障害となっている．現在，大腸癌肝転移，肺転移に対し根治可能な治療はそれぞれ外科的切除のみであり，肝転移肝切除，肺転移肺切除は積極的に施行されている．

同一症例において肝転移と肺転移が引き続いてもしくは同時に認められることもまれではない．肝転移，肺転移に対する切除の適応は拡大傾向にあり，肝・肺転移症例に対する外科切除の報告も認められるようになっている．

キーワード：大腸癌，肝転移，肺転移，切除

* Surgical treatment for hepatic and pulmonary metastases from colorectal cancer

** S. Takahashi, T. Kinoshita(外来部長)〈上腹部外科〉, K. Nagai(医長)〈胸部外科〉, N. Saito(手術部長)〈骨盤外科〉：国立がんセンター東病院(〒277-8577　柏市柏の葉6-5-1)．

本稿では，過去に報告された大腸癌肝・肺転移外科的切除の成績をレビューするとともに，とくに切除適応の問題となる肝・肺同時転移例に対する当院の切除成績を供覧する．

I. 大腸癌肝転移，肺転移に対する切除

1. 大腸癌肝転移に対する肝切除

肝切除は，最近20年で大腸癌肝転移に対する第一選択治療として確立された．肝切除 vs 非外科的治療のRCTこそ倫理的問題から施行されていないが，根治切除例では5年，10年以上の長期生存を認めるにもかかわらず，切除不能例では認められないことから，その有効性は明らかである[2]．過去に行われた大腸癌肝転移肝切除のlarge studyでは，5年生存率が25～50%程度と報告されている[3,4]．手術法や術前・術後管理の進歩により肝切除の安全性が増し，切除適応は拡大の傾向にある．

2. 大腸癌肺転移に対する肺切除

大腸癌肺転移に対する肺切除は，Blalockらにより1944年にはじめて報告され[5]，1965年には

Thomfordらにより切除の適応が提唱されている[6]．その適応は，「肺以外に遠隔転移を認めない異時性の肺転移であり，原発巣が十分にコントロールされ，安全に手術が施行可能な症例」とされている．大腸癌，とくに結腸癌の場合，転移経路を考えると肺は肝より遠位にあり，肺転移は肝転移より進行した状態と考えることもできる．また，明らかなエビデンスはないが「肺転移は肝転移巣からの転移である」というcascade theoryの存在もあり[7]，肺転移に対する肺切除は当初はかなり限られた症例に施行されていた．

しかし現在にいたるまで，切除以外に根治的な治療が存在しないことから肺転移に対しても切除が積極的に行われるようになっている．Thomfordの適応にとらわれず切除を施行している施設も多くなっているが，最近の報告では肺切除後5年生存率は21～56%と肝切除後の予後とほぼ同様の結果であった[8~10]．現在，大腸癌肺転移肺切除の適応にゴールデンスタンダードはなく，「すべての転移巣が切除可能で，術後心肺機能が保持される症例」としている施設もある．

II. 大腸癌肝・肺転移に対する外科的切除

遠隔転移を2臓器(肝臓と肺)に認める状態は，肝転移もしくは肺転移のみの場合と比較し，より進行した状態であると推測され，病変自体は切除可能であったとしても，先に述べたThomfordらの適応にあるように切除の対象からはずされることが多かった．しかし，手術の安全性が向上し，いまだに手術以外に根治的な治療がみつからない状況において，肝転移，肺転移に対する手術適応は拡大しており，大腸癌肝・肺転移に対する外科的切除も限られた症例に対してではあるが行われ，その有効性が報告されている．

1. 切除成績(表1)

胸部外科から，肝転移切除後の異時性肺転移肺切除例の成績が報告されている．Regnardらは，肝転移切除後の異時性肺転移肺切除43例の成績を報告しており，5年生存率，10年生存率はそれぞれ11%，0%と肺転移単独切除例の27%，17%と比較すると低いが，両群間に明らかな差を認めていない[11]．またHeadrickらも，肝転移切除後異時性肺転移肺切除を中心とした大腸癌肝・肺転移例の切除成績を報告しているが，5年生存率，10年生存率はそれぞれ30%，16%と比較的良好な結果を得ている[12]．多施設のデータをretrospectiveに検討したSaitoらのstudyによれば，肝転移切除後異時性肺転移肺切除26例の予後(5年生存率34.1%，10年生存率34.1%)は肺転移単独切除139例の予後(5年生存率40.6%，10年生存率37.5%)とほぼ同等であった[9]．当施設(Watanabeら)における大腸癌肺転移肺切除49例の検討でも肝転移肝切除の既往は予後に影響を与えていない[10]．

腹部外科からは，肝転移切除後異時性肺転移だけでなく，肺転移切除後異時性肝転移と肝・肺同時転移に対する外科的切除も含めた成績が報告されている．Murataらは，肝転移切除後異時性肺転移肺切除17例，肺転移切除後異時性肝転移肝切除1例と肝・肺同時転移切除12例の計30例の成績を検討しているが，全体の5年生存率は43.8%と比較的予後良好であった[13]．Nagakuraらの検討によれば，肝転移切除後異時性肺転移肺切除16例，肺転移切除後異時性肝転移肝切除1例，肝・肺同時転移切除10例，計27例の術後5年生存率は27%，生存期間中央値が32ヵ月であった[14]．

以上の成績を考慮すると，大腸癌肝・肺転移例の中には切除により長期生存が得られるサブグループが確実に存在するといえる．

2. 手術の安全性

大腸癌肝・肺転移切除の問題点として周術期のmorbidity，mortalityがあげられることが多い．しかし，上記の検討ではmorbidityは5～12%，mortalityはいずれも0%であり，慎重に患者選択を行えば安全性については大きな問題はない．

3. 手術適応，予後因子

Murataらは，大腸癌肝・肺転移に対する切除適応を「原発巣が十分にコントロールされ，肝・肺以外に遠隔転移を認めず，すべての転移巣が安全に切除可能であり，術後，肝機能，心肺機能が保持可能な症例」としている．他の報告もほぼ同

表1. 大腸癌肺・肝転移に

報告者(年)	症例数(肝・肺異時転移/同時転移例)	morbidity(%)
Murata ら[13] (1998)	30(18/12)	10
Regnard ら[11] (1998)	43(43/0)	5
Headrick ら[12] (2001)	58(52/6)	12
Nagakura ら[14] (2001)	27(17/10)	—
当施設	21(13/8)	9.5

様であり，われわれの施設も同様である．しかし，どのような病変まで切除の対象にいれるのか，施設間で相違があると思われ，切除の上限は定まっていないと考えられる．

肝・肺転移という病態を考慮すると，切除の適応には十分に慎重でなくてはならない．なぜなら，2臓器に転移があるということは，1臓器よりもsystemic diseaseとしての性格が強いこと，また生物学的悪性度が高い可能性が否定できないからである．上記検討で明らかになった予後不良因子をあげてみると，肺切除術前CEA値5 ng/ml以上，肺の複数箇所切除，縦郭リンパ節転移，原発巣との同時性転移，両葉肺転移，60歳以上，肝・肺同時転移などであった．いずれの検討もsmall populationのretrospective studyであり，絶対的な予後不良因子とまではいいがたいが，これらの因子を認める場合は，慎重に手術の適応を検討する必要があろう．

III. 肝・肺同時性転移に対する切除

「肝・肺同時転移」は臨床的に重要な問題であり，前述の予後因子の一つにもあがっており，実際に手術の適応に迷う(または適応からはずしている)臨床医が多いのではないであろうか．大腸癌肝・肺異時性転移に対する切除の意義についてはコンセンサスが得られ始めているが，肝・肺同時転移に対する切除はまだcontroversialといえる，

上述したNagakuraらの検討では，肝転移と肺転移が同時にみつかった症例は異時性にみつかった症例と比較し予後が不良であり，肝・肺同時転移は大腸癌肝・肺転移切除後の有意な予後不良因子であった〔RR(relative risk)=12.7，CI(confidence interval)=3.08～52.3，$p<0.001$〕と報告している．

当施設においても，大腸癌肝・肺同時転移例に対する切除の意義を検討するため，当施設で肝，肺切除を施行した21例の検討を行っている[15]．

21例のうち，肝・肺同時転移例が8例，肝・肺異時転移例が13例であり，2群間の臨床病理学的諸因子(結腸/直腸，Dukes分類，腫瘍分化度，肝・肺転移巣の腫瘍径，個数，distribution，術前CEA)に有意な差は認めていない．

肝切除は，2例に葉切除，3例に区域切除，16例に亜区域切除・部分切除が施行され，肺切除は，1例にpneumonectomy，3例に葉切除，17例に区域切除・部分切除が施行された．肝・肺同時転移例の手術の順序は，より進行した転移に対し切除を先行する施設もあるが，当施設では腹膜転移，局所再発など腹腔内の腫瘍状況が確認でき肺合併症軽減にも有利なため，肝切除を先行した後肺切除としている．切除された肝病変は平均腫瘍数1.7個，平均腫瘍径2.8 cm，両葉転移5例であり，肺病変は平均腫瘍数1.4個，平均腫瘍径2.4 cm，両葉転移2例であった．Morbidity 9.5%，mortality 0%と安全に手術が施行され，全21例の5年生存率も54.3%と良好な成績が得られている．

肝転移・肺転移の出現時期が予後に及ぼす影響を検討するため，肝・肺同時転移例と肝・肺異時転移例の予後を検討したが，術後生存に有意な差を認めず(図1)，同時転移例にも5年以上の長期生存例2例を認めた．21例と症例数の少ない検討ではあるが，異時性だけでなく同時転移例に対する切除も意義がある可能性が示された．この検討

対する外科的切除の成績

mortality(%)	5年生存率(%)	予後不良因子
0	43.8	原発巣との同時性転移，両葉転移(肺)
0	11	肺切除術前CEA値5ng/ml以上，複数箇所切除(肺)
0	30	肺切除術前CEA値5ng/ml以上，胸部リンパ節転移
—	27	60歳以上，肝・肺同時転移
0	54.3	—

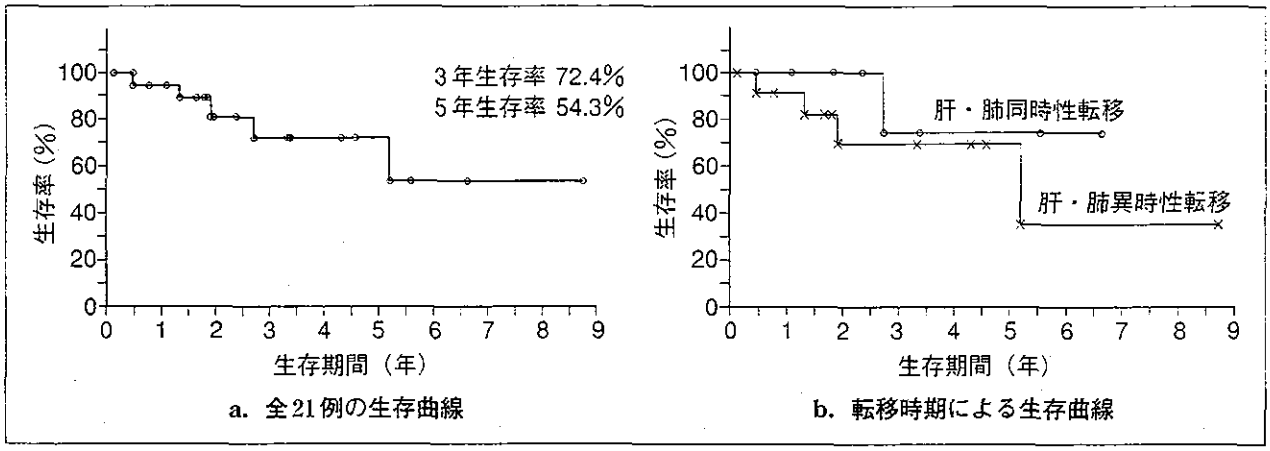

図1．大腸癌肝・肺転移切除後生存曲線
生存日数は，後に施行した手術日から起算

表2．臨床病理学的因子と生存期間の相関(単変量解析)

因　子	hazard ratio(95%信頼区間)	p
原発巣リンパ節転移陽性	7.89(0.84 ~ 74.1)	0.07
原発巣直腸	0.50(0.08 ~ 3.15)	0.46
肝転移腫瘍径3cm以上	1.17(0.19 ~ 7.09)	0.86
肝転移2個以上	2.03(0.22 ~ 18.9)	0.53
肝両葉転移	0.67(0.08 ~ 6.07)	0.73
肺転移腫瘍径3cm以上	0.59(0.06 ~ 5.62)	0.65
肺病変2個以上	2.07(0.34 ~ 12.5)	0.43
肺両葉転移	3.38(0.35 ~ 32.9)	0.29
術前CEA値50ng/ml以上	0.87(0.10 ~ 7.77)	0.87
肝切除と肺切除のinterval 1年未満	1.14(0.12 ~ 11.1)	0.91
原発巣と最初の転移巣切除のinterval 1年未満	0.84(0.14 ~ 5.14)	0.85
肝肺同時転移	0.34(0.04 ~ 3.07)	0.34

では，さらに11の臨床病理学的諸因子について予後との相関を検討したが，有意な相関を認めていない(表2)．

今後も異時性，同時性を問わず大腸癌肝・肺転移切除の症例を重ね，手術適応のさらなる検討を行う必要があると考えている．

おわりに

大腸癌肝・肺転移はlocalized diseaseとsystemic diseaseの狭間にある疾患である．どのような症例がlocalized diseaseに近く切除が有効なのかみきわめ，手術適応を確立する必要がある．また，治療成績向上のため，術前もしくは術後全身化学療法の有効性を検討する必要があるであろう．Prospective studyはむずかしいかもしれないが，個々の施設では症例数に限りがあるため多施設共同による検討が必要であると考える．

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ORIGINAL ARTICLE

Ayumu Hosokawa · Yasuhide Yamada · Yasuhiro Shimada · Kei Muro · Tetsuya Hamaguchi · Hideko Morita · Mari Araake · Hiromi Orita · Kuniaki Shirao

Prognostic significance of thymidylate synthase in patients with metastatic colorectal cancer who receive protracted venous infusions of 5-fluorouracil

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Abstract

Background. This study was conducted to evaluate the prognostic significance of thymidylate synthase (TS) expression in the tumor tissue of patients with metastatic colorectal cancer (CRC) who received protracted venous infusions of 5-fluorouracil (5-FU).

Methods. We retrospectively analyzed the prognostic value of TS expression as compared with other clinical prognostic factors in 57 patients with metastatic CRC.

Results. On univariate analysis, survival was significantly related to TS expression (low vs high; $P = 0.0015$), alkaline phosphatase (ALP) level (<300 vs ≥300 IU/l; $P = 0.0037$), performance status (0 or 1 vs 2 or 3; $P = 0.0073$), and white blood cell count (<10000/mm^3 vs >10000/mm^3; $P = 0.0001$), with number of metastatic sites (1 vs ≥2; $P = 0.06$) approaching significance. On multivariate analysis, survival was significantly related to TS expression (hazard ratio [HR], 2.97) and ALP level (HR, 2.26).

Conclusion. In patients with metastatic CRC who received protracted venous infusions of 5-FU, TS expression was related to survival independently of other established clinical prognostic factors.

Key words Colorectal cancer · Fluorouracil · Prognostic factor · Continuous infusion · Thymidylate synthase

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the world and the third most fatal malignant neoplasm in Japan. The mainstay of drug treatment for metastatic CRC for more than 40 years has been 5-fluorouracil (5-FU). Protracted continuous infusion of 5-FU was initially proposed by Lokich et al.,[1] and a recent meta-analysis comparing continuous infusion of 5-FU with bolus injection found that the patients with protracted infusional therapy had a higher response rate and longer survival. Furthermore, prolonged exposure to stable levels of 5-FU reduced the associated hematologic toxicity.[2] Although recent clinical trials of combination therapy with irinotecan or oxaliplatin have demonstrated improved survival, 5-FU remains one of the most important drugs for the treatment of metastatic CRC.

Various clinical variables, including performance status (PS), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), white blood cell (WBC) count, hemoglobin level, histologic grade, and tumor markers such as carcinoembryonic antigen (CEA) are recognized prognostic factors in advanced CRC.[3–5] Köhne et al.[6] reported that PS, WBC count, ALP, and the number of metastatic sites were useful clinical predictors of survival in a large series of patients who received 5-FU-based treatment for CRC.

Thymidylate synthase (TS), the primary intracellular target enzyme for the fluoropyrimidine class of chemotherapeutic agents, has been studied as a prognostic marker of fluoropyrimidine-based therapy.[7,8] To our knowledge, however, no study has evaluated whether TS is related to survival independently of recognized prognostic factors in advanced CRC.

In the present investigation, we retrospectively examined the prognostic significance of TS expression and other clinical variables in 57 patients with metastatic CRC who received protracted venous infusions of 5-FU.

Patients and methods

Patients

Fifty-seven patients with metastatic CRC who received protracted venous infusions of 5-FU between January and

A. Hosokawa · Y. Yamada (✉) · Y. Shimada · K. Muro · T. Hamaguchi · H. Morita · M. Araake · H. Orita · K. Shirao
Gastrointestinal Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3545-3567
e-mail: yayamada@ncc.go.jp

December 1998 at the National Cancer Center Hospital were studied retrospectively. All patients had (1) metastatic or relapsed CRC, confirmed pathologically; (2) PS (Eastern Cooperative Oncology Group) of 0 to 3; (3) received none or one previous course of chemotherapy; (4) no severe coexistent disease; and (5) available tumor samples.

Treatment

All patients received 5-FU intravenously at a dose of 200 to 250 mg/m^2 daily. The drug was delivered through a central venous catheter connected to a Surefuser A 50-ml disposable pump (balloon infusional pump purchased from Nipro, Tokyo, Japan) or an electric ambulatory pump. Treatment was discontinued if grade 2 or more severe treatment-limiting toxicity developed, such as mucositis, diarrhea, hand-foot syndrome, or hematological toxicity, according to World Health Organization (WHO) criteria. The infusion was interrupted until resolution of the toxicity and then resumed at the same dose. Treatment was terminated if progressive disease was confirmed or if the patient refused to continue therapy.

Response and survival

Tumor response was evaluated according to the WHO criteria in patients with metastatic CRC who had assessable measurable lesions other than peritoneal and bone metastasis. Overall survival time was measured from the date of the initial treatment until the time of the last follow-up visit or death.

TS staining

Immunohistochemical studies were performed by the avidin-biotin complex immunoperoxidase technique. Paraffin-embedded tissue was cut into 4-μm-thick sections. The specimens of 44 primary tumors and 13 liver metastases resected from 57 patients with advanced CRC were analyzed immunohistochemically. After deparaffinization in xylene, the sections were hydrated through a series of graded alcohols and distilled water. Slides of the sections were placed in methanol containing 0.3% hydrogen peroxidase for 20 min at room temperature to block endogenous peroxidase activity.

The slides were then immersed in 10 mmol/l citrate buffer, pH 6.0, autoclaved at 121°C for 15 min, and cooled at room temperature for 20 min. After the sections were incubated with normal horse serum (Vector, Burlingame, CA, USA) for 30 min to block nonspecific antibody binding sites, primary antibody was applied, and the sections were incubated overnight at 4°C in a high-humidity chamber. The primary antibody used for immunohistochemical analysis was anti-human TS polyclonal antibody.[9] After three washes with phosphate-buffered saline (PBS), the slides were incubated with a 1:200 dilution of biotinylated horse anti-mouse/anti-rabbit IgG (Vector) for 30 min, washed three times with PBS, and incubated with avidin-biotin-peroxidase complex (Vector) for 60 min. Peroxidase staining was performed for 3–5 min, using a solution of 3,3'-diaminobenzidine tetrahydrochloride in Tris-buffered saline (TBS) containing 0.01% hydrogen peroxide. The sections were counterstained with Mayer's hematoxylin for 10 s, dehydrated in a series of ethanol, cleared in xylene, and mounted under a cover slip with a permanent mounting medium. Sections known to stain positively were included in each run as positive controls. Negative control sections were processed without the primary antibody.

All samples were read blindly. TS expression was quantified according to a visual grading system based on the intensity of staining and was arbitrarily classified into high and low groups according to the visual grading system.[10] The highest staining intensity found in a tumor was used for classification. The agreement of TS intensity scoring reached by two independent observers was greater than 90%. When there was disagreement, intensity was determined by consensus.

Statistical analysis

The χ^2 test, Fisher's exact test, and Student's *t*-test were used to compare clinicopathologic features, including low and high TS expression. Survival was estimated by the Kaplan-Meier method, and statistical differences were determined by the log-rank test. The variables included in univariate survival analysis were PS, ALP, WBC count, number of metastatic sites, and TS expression. Multivariate analysis was performed using Cox's proportional-hazards model. All calculations were performed with the use of the Stat View J-5.0 statistical software package (SAS Institute, Cary, NC, USA). *P* values of 0.05 or less were regarded as significant.

Results

Included in the present study were 57 patients with a median age of 59 years. Twenty-four patients had received prior chemotherapy. Twelve patients had been treated with hepatic arterial infusion of 5-FU, 8 patients with oral fluoropyrimidines such as uracil/tegafur or 5'-deoxy-5-fluorouridine, and 4 patients with 5-FU and irinotecan. TS expression was high in 25 tumors (44%) and low in 32 tumors (56%). The relation between clinicopathologic features and TS expression is summarized in Table 1. No significant differences in clinicopathologic features were found between patients with low and those with high TS expression.

The median treatment period in the 57 patients was 169 days (range, 28–1269 days). There was no treatment-related death. Fifty-three patients were assessable for response to chemotherapy. An objective response was seen in 16 of the 53 patients with assessable disease (30%; 95% confidence interval, 22%–38%), including 2 (4%) complete responses.

Table 1. Relation between clinicopathologic features and thymidylate synthase (TS) expression

	No. of patients		*P* Value
	TS high (n = 25)	TS low (n = 32)	
Age (years)			0.83
<60	14	17	
≧60	11	15	
Sex			0.90
Male	16	21	
Female	9	11	
Location of tumor			0.49
Colon	15	22	
Rectum	10	10	
ECOG performance status			0.59
0 or 1	18	25	
2 or 3	7	7	
Tumor differentiation			0.99
Adenocarcinoma			
Well	12	15	
Moderately	12	16	
Poorly	1	1	
Tumor sample			0.35
Primary tumor	21	23	
Liver	4	9	
Number of metastatic sites			0.27
1	13	12	
≧2	12	20	
No. of prior chemotherapy regimens			0.17
0	17	16	
1	8	16	
WBC count (per mm^3)			0.087
<10000	18	29	
≧10000	7	3	
ALP (IU/l)			0.55
<300	9	14	
≧300	16	18	

ECOG, Eastern Cooperative Oncology Group

The median survival time (MST) for all patients was 365 days; 1- and 2-year survival rates were 54% and 25%, respectively. Survival curves for the patients with low TS expression and those with high TS expression are shown in Fig. 1. There was a significant difference between the two groups; the MST was 553 days in the patients with low TS expression and 237 days in those with high TS expression (P = 0.0015). We investigated for a correlation between TS expression and the response to protracted venous infusion of 5-FU; however, TS expression did not significantly correlate with the clinical response to this treatment. The response rates were 37% (11/30) in the low-TS group and 22% (5/23) in the high-TS group (P = 0.366).

Five variables were included in the univariate analysis to determine their relation to survival. Significant predictors of poor survival were high TS expression, an ALP level of 300IU/l or higher, a PS of 2 or 3, and a WBC count of 10000/mm^3 or higher.

The four variables significantly related to survival on univariate analysis were entered in multivariate regression

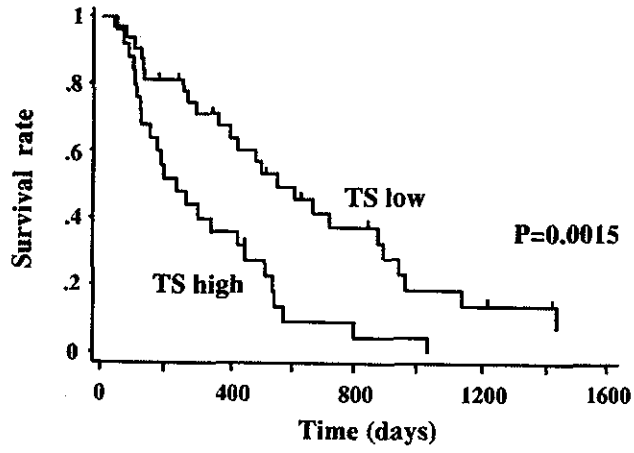

Fig. 1. Survival and the expression of thymidylate synthase (*TS*). Cumulative Kaplan-Meier survival curves according to TS expression in 57 patients with metastatic colorectal cancer (CRC) who received protracted venous infusions of 5-fluorouracil (FU)

Table 2. Univariate and multivariate analyses of possible prognostic factors for survival

Variable	Univariate analysis	Multivariate analysis		
	P Value	HR	95% CI	*P* Value
TS expression				
Low		1		
High	0.0015	2.97	1.45–6.08	0.0028
ALP				
<300IU/l		1		
≥300IU/l	0.0037	2.26	1.11–4.61	0.025
Number of metastatic sites				
1				
≥2	0.060			
PS				
0 or 1		1		
2 or 3	0.0073	1.60	0.77–3.30	0.21
WBC (per mm^3)				
<10000		1		
≥10000	0.0001	1.46	0.57–3.73	0.43

HR, hazard ratio; 95% CI, 95% confidence interval; TS, thymidylate synthase

analysis, using the Cox proportional-hazards model. TS expression and ALP level were found to be independent and significant predictors of survival in the Cox model (hazard ratios, 2.97 and 2.26, respectively; Table 2).

Discussion

The clinical significance of TS expression in surgically resected tissue specimens was examined in 57 patients with metastatic CRC who received protracted venous infusions of 5-FU. Our results showed that the MST of patients with low TS expression was longer than that in patients with high TS expression. Moreover, multivariate analysis demonstrated that the intensity of TS expression was an independent (and the strongest) prognostic factor.

A number of prognostic factors have been linked to the outcome of 5-FU-based chemotherapy in patients with metastatic CRC. Previous studies have shown that PS is one of the most significant predictors of survival.[11–15] Other prognostic factors are also associated with the outcome of metastatic CRC, including LDH,[5] ALP,[16] WBC count,[11,12] serum albumin level,[12,15] hemoglobin level,[13,14] pathological grade,[17] CEA,[11,17] and number of metastatic sites.[11] Köhne et al.[6] reported that PS, WBC count, ALP, and number of metastatic sites were useful clinical predictors of survival in 3825 patients given 5-FU-based treatment for metastatic CRC. Thus, we included these four clinical variables in our multivariate model.

Many studies have attempted to identify new biochemical and molecular predictors of survival, such as TS, P53, and dihydropyrimidine dehydrogenase (DPD). Among these biochemical markers, TS has been demonstrated in several studies to be a potentially valuable prognostic marker of the response to 5-FU-based chemotherapy.[7,8,18] To our knowledge, no previous study has examined whether TS is an independent prognostic factor, unaffected by established common clinical predictors of survival in advanced CRC. New molecular or biological markers should be validated against established clinical variables. We found that high TS expression was a potent predictor of shorter survival on univariate analysis and an independent prognostic factor on multivariate analysis.

Although TS expression did not significantly correlate with the clinical response, responders were seen more often among the patients with low TS expression compared with those with high TS expression, i.e., 37% (11/30) in the low-TS group and 22% (5/23) in the high-TS group. Our study was not a randomized trial, but a retrospective study. Thus, small sample size and some selection biases in the present population may have contributed to the outcome; however, low-TS cancer may be slow-growing and biologically less malignant compared with high-TS cancer, regardless of the presence of 5-FU infusion therapy.

In conclusion, our results showed that high TS expression in tumor tissue was an independent prognostic factor in patients with metastatic CRC who received protracted venous infusions of 5-FU.

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ORIGINAL ARTICLE

**Ayumu Goto · Yasuhide Yamada · Ayumu Hosokawa
Takashi Ura · Tatsuhiro Arai · Tetsuya Hamaguchi
Kei Muro · Yasuhiro Shimada · Kuniaki Shirao**

Phase I/II study of irinotecan, 5-fluorouracil, and *l*-leucovorin combination therapy (modified Saltz regimen) in patients with metastatic colorectal cancer

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Abstract

Background. A combination of irinotecan 125 mg/m^2, 5-fluorouracil (5-FU) 500 mg/m^2, and leucovorin (LV) 20 mg/m^2 (Saltz regimen; treatment on days 1, 8, 15, and 22 every 6 weeks) is widely used for the treatment of metastatic colorectal cancer. A modified schedule with chemotherapy on days 1 and 8 of a 21-day cycle was recommended in 2001 because of early treatment-related mortality. We conducted a phase I/II study of this modified Saltz regimen as first-line therapy in Japanese patients with metastatic colorectal cancer to assess the maximum tolerated dose (MTD) and the recommended dose of 5-FU when given with fixed doses of *l*-LV and irinotecan, and to evaluate the efficacy and the feasibility of this regimen.

Methods. Irinotecan, 5-FU, and *l*-LV were administered on days 1 and 8 of a 21-day cycle. Irinotecan 100 mg/m^2 was given intravenously over the course of 90 min on day 1, followed by *l*-LV 10 mg/m^2, and then 5-FU. The dose of 5-FU was escalated from 400 mg/m^2 (level 1) to 500 mg/m^2 (level 2). If neither level met the criteria for the MTD, the recommended dose was defined as level 2, and dose escalation was discontinued, because the maximum approved weekly dose of irinotecan alone in Japan is 100 mg/m^2 and the dose of 5-FU in the original Saltz regimen was 500 mg/m^2.

Results. One patient had grade 4 neutropenia with fever at level 1, and four patients had grade 3 neutropenia at level 2. There was no treatment-related death. Level 2 did not meet the criteria for the MTD. The relative dose intensities of the first five cycles were 91% for both 5-FU and irinotecan at level 1 and 86% for 5-FU and 93% for irinotecan at level 2. The response rates were 58% for all patients, and 69% for patients at level 2.

Conclusion. Our results confirm that the modified Saltz regimen is safe and efficacious for Japanese patients. The recommended doses for phase II studies are irinotecan 100 mg/m^2, 5-FU 500 mg/m^2, and *l*-LV 10 mg/m^2.

Key words Colorectal cancer · 5-Fluorouracil · Irinotecan · *l*-Leucovorin · Phase I/II study

A. Goto · Y. Yamada (✉) · A. Hosokawa · T. Ura · T. Arai · T. Hamaguchi · K. Muro · Y. Shimada · K. Shirao
Gastrointestinal Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. 81-3-3542-2511; Fax +81-3-3542-3815
e-mail: yayamada@ncc.go.jp

Introduction

A combination of 5-fluorouracil (5-FU) and leucovorin (LV), the standard first-line therapy for advanced colorectal cancer for two decades, has a response rate of only 23% and a median survival time (MST) of 11.5 months.[1] Irinotecan is a potent inhibitor of topoisomerase I. In randomized phase III trials, irinotecan extended survival significantly as compared with best supportive care or 5-FU infusion when given as second-line therapy.[2,3] Moreover, two other randomized phase III trials showed that a combination of irinotecan, 5-FU, and LV had higher response rates, a longer time to progression (TTP), and better overall survival than did 5-FU/LV therapy.[4,5] The MST in patients who received this three-drug therapy was 14.8–17.4 months.

This three-drug regimen was designated one of the standard first-line treatments for metastatic colorectal cancer in the United States and Europe. However, patients who received a combination of irinotecan, bolus 5-FU, and LV had a three fold higher rate of early treatment-related mortality (2.5%–3.5%) from gastrointestinal toxicity or thromboembolic events compared with patients who received 5-FU/LV or oxaliplatin-based regimens (0.8%–1.1%) in subsequent phase III trials (Cancer and Leukemia Group B protocol C89803 and North Center Cancer Treatment Group protocol N9741).[6]

Irinotecan 125 mg/m^2, 5-FU 500 mg/m^2, and LV 20 mg/m^2 are given on days 1, 8, 15, and 22 every 6 weeks in

the original Saltz regimen. In 2001, several investigators questioned how many patients received the Saltz regimen without dose reductions. The percentages of patients given irinotecan, 5-FU, and LV therapy who received the recommended doses of irinotecan and 5-FU were as follows: 89% and 88% on day 8, 64% and 64% on day 15, and 45% and 45% on day 22 of cycle 1; 47% and 48% on day 1 of cycle 2; and 42% and 41% on day 1 of cycle 3.[7] Subsequently, Elfring et al.[8] reported, in a United States study, phase III that patients received median doses of 418 mg/m^2 of irinotecan and 1602 mg/m^2 of 5-FU in the original Saltz regimen[1] during the first cycle. Knight et al.[9] recommended that the treatment schedule be modified to days 1 and 8 of a 21-day cycle, or that the initial dosage of cycle 1 be revised to irinotecan 100 mg/m^2, 5-FU 400 mg/m^2, and LV 20 mg/m^2. However, the feasibility of these modified regimens has not been studied in Japan, and many patients with colorectal cancer continue to receive 5-FU/l-LV as first-line therapy.

The present phase I/II study was designed to evaluate the safety and efficacy of a modified Saltz regimen (treatment on days 1 and 8 of a 21-day cycle) and to determine the recommended dose (RD) of irinotecan in combination with 5-FU/l-LV in Japanese patients with colorectal cancer.

Patients and methods

Eligibility

Eligible patients had histologically confirmed metastatic colorectal adenocarcinoma with measurable disease, defined as the presence of at least one index lesion able to be measured on computed tomographic (CT) scans. Other eligibility criteria included age between 20 and 75 years; Eastern Cooperative Group (ECOG) performance status of 0–2; adequate baseline bone marrow (white blood cell (WBC) count between 4000 and 12000/μl and platelets more than 100000/μl), suitable hepatic function (serum bilirubin level, 1.1 mg/dl or less, and serum aspartate aminotransferase and alanine aminotransferase 100 U/l or less), and suitable renal function (serum creatinine level, 1.2 mg/dl or less); and the ability to orally ingest food and liquids. Patients who had received prior irinotecan, bolus 5-FU therapy, or pelvic radiotherapy were excluded. Patients could have previously received adjuvant fluoropyrimidine-based chemotherapy, provided that such therapy had been terminated at least 4 weeks before study entry. Patients were also excluded if they had severe pleural effusion, ascites, diarrhea, uncontrolled infection, symptomatic brain metastases, bowel obstruction, or a high risk of a poor outcome because of concomitant uncontrollable non-malignant disease, such as diabetes, cardiac failure, or renal failure. Pregnant or breast-feeding women were also excluded. This study was approved by the institutional review board. All patients gave written informed consent before enrollment.

Treatment plan and dose escalation

Eligible patients received the following regimen: irinotecan 100 mg/m^2 by 90-min intravenous infusion; followed by *l*-LV 10 mg/m^2, administered over the course of 15 min; and 5-FU, given by bolus intravenous injection after *l*-LV. The three drugs were given on days 1 and 8 of a 21-day cycle. 5-FU was given at a dose of 400 mg/m^2 for level 1 or 500 mg/m^2 for level 2. All patients routinely received 3 mg of granisetron plus 8 mg dexamethasone before the irinotecan. Treatment continued until disease progression, unacceptable toxicity, or patient refusal.

Dose-limiting toxicity (DLT) was defined as any of the following findings during cycle 1 or 2: grade 3 non-hematologic toxicity other than nausea, vomiting, anorexia, fatigue, and hyponatremia; grade 4 leukopenia lasting for 5 days; grade 3 febrile neutropenia; grade 4 thrombocytopenia or grade 3 thrombocytopenia with hemorrhage; a WBC count of less than 3000/μl; a platelet count of less than 100000/μl, or non-hematologic toxicity of grade 2 or higher on day 22, requiring treatment to be discontinued for at least 8 days. Patient cohorts comprised a minimum of three patients for each dose level. If all three patients at level 1 completed two cycles of treatment without DLT, the next three patients were entered at level 2. If one of the three patients had DLT, three additional patients were recruited at the same dose level. If two of three or three of six patients had DLT, the maximum tolerated dose (MTD) was defined as the dose level given to this cohort. Dose reduction was not permitted during the first two cycles. If DLT occurred at level 1, the dose of irinotecan was reduced to 75 mg/m^2 from cycle 3 onward. The RD was defined as the dose one level below the MTD. If neither level 1 nor level 2 met the criteria for the MTD, the RD was defined as level 2, and dose escalation was discontinued, because the maximum approved weekly dose of irinotecan alone in Japan is 100 mg/m^2 and the dose of 5-FU in the original Saltz regimen was 500 mg/m^2. After determination of the RD, 14 patients were additionally enrolled to confirm tolerability.

Patient evaluation

Toxicity was assessed according the National Cancer Institute common toxicity criteria (NCI-CTC), version 2.0.[10] Pretreatment evaluation included a clinical examination, complete blood cell count (CBC), and chemistry profile. During treatment, toxicity was assessed weekly during cycle 1 and on days 1 and 8 of subsequent cycles.

Dose intensity was calculated by dividing the total dose received by the patient by the total duration of treatment, expressed in weeks. Relative dose intensity was calculated by dividing the delivered dose intensity by the dose intensity planned according to protocol. Dose intensity was defined within a maximum of five cycles for each patient.

The responses of assessable disease sites were evaluated according to the *New guidelines to evaluate the response to treatment in solid tumors* (RECIST).[11] Assessable lesions were reassessed every 8 weeks by CT scanning.

Results

Patient characteristics

A total of 20 patients were enrolled between January and October 2002 at the National Cancer Center Hospital. Table 1 shows the baseline characteristics of the patients. Only 1 patient had received adjuvant therapy with an oral fluoropyrimidine derivative 1 month before study entry.

There was a deviation from the protocol in one patient, who withdrew his consent during therapy. This patient had received a lower anterior resection for primary rectal cancer and had continuous mild anal bleeding. After cycle 1, he requested to be transferred to another other hospital for treatment of the anal bleeding and refused to continue chemotherapy (not considered DLT).

DLT and RD

Nine patients (six at level 1 and three at level 2) received at least two cycles of treatment for dose-finding. Adverse events occurring during the first two cycles of treatment, used to estimate the MTD, are shown in Tables 2 and 3.

Table 1. Patient characteristics

No. of patients	20
Male/female	15/5
Performance status (ECOG) 0/1	17/3
Age (years)	
Median	61
Range	32–71
Primary site	
Rectum	10
Colon	10
No. of metastatic sites 1/2/3	14/5/1
Metastatic sites	
Lung	10
Liver	9
Lymph nodes	6
Peritoneum	2
Pleura	1
Previous treatment	
Adjuvant oral fluoropyrimidine	1
None	19

ECOG, Eastern Cooperative Group

Three patients were treated at level 1 with 5-FU 400 mg/m^2. One of these patients had grade 4 neutropenia with fever on day 15 of cycle 1. This patient was a 54-year-old woman with multiple lung metastases and a *performance* status of 0. The results of physical examination, CBC, and chemistry profile were normal at entry, although the serum total bilirubin level 2 weeks before entry (1.2 mg/dl) had been slightly above the upper limit of normal. Chemotherapy was not given to this patient on day 8 of cycle 1 because of neutropenia. She received antibiotics and granulocyte colony-stimulating factor for the remainder of cycle 1. All adverse events resolved by day 1 of cycle 2, and the chemotherapy was resumed. However, the patient had grade 2 diarrhea on day 8 and grade 2 neutropenia on day 15 of cycle 2, indicating inability to tolerate irinotecan in combination with 5-FU and *l*-LV. Bolus 5-FU and *l*-LV were therefore given subsequently. Three additional patients were then assigned to receive level 1. The other five of the six patients given level 1 completed two cycles of treatment without severe toxicity.

The three patients who initially received level 2 (5-FU 500 mg/m^2) had no DLT. Level 2 was therefore designated as the RD. Eleven other patients received level 2 to confirm adverse events and efficacy. One of these patients had moderate hepatic dysfunction, probably related to a nutritional supplement. In this patient, treatment scheduled for day 1 of cycle 2 was postponed for 6 weeks. Apart from this deviation from protocol, no DLT occurred in any of the 14 patients given level 2.

Toxicity

Toxicity was recorded for all patients who received one to five cycles of chemotherapy (total, 75 cycles) (Table 4). The most common type of hematologic toxicity was neutropenia. All grade neutropenia and grade 3/4 neutropenia, respectively, occurred in 42 (56%) and 7 (9%) of the 75 cycles administered. The hemoglobin level decreased slightly in 61 (81%) of the 75 cycles, with no grade 3/4 anemia. The baseline hemoglobin level in nearly all patients was grade 1 or the lower limit of normal before the start of treatment. Thrombocytopenia did not occur in any cycle.

The most frequent type of non-hematologic toxicity was fatigue. Grade 1/2 fatigue occurred in 45 (60%) of 75 cycles; no grade 3/4 fatigue was reported. Anorexia occurred in 24

Table 2. Hematologic toxicity in the first two cycles

	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3, 4 (%)
Level 1 (n = 6)					
Leukopenia	1	2	1	0	17
Neutropenia	2	0	0	1	17
Hemoglobin decrease	4	1	0	0	0
Thrombocytopenia	0	0	0	0	0
Level 2 (n = 14)					
Leukopenia	5	1	2	0	14
Neutropenia	1	3	4	0	29
Hemoglobin decrease	10	1	0	0	0
Thrombocytopenia	0	0	0	0	0

(32%) and nausea in 22 (29%) of 75 cycles. Grade 1/2 mild diarrhea developed in 18 (24%) of 75 cycles. Stomatitis occurred in 8 (11%) of 75 cycles. Infection, with grade 4 neutropenia, occurred in 1 of 75 cycles. There was no treatment-related mortality. No patient who received up to five cycles of chemotherapy had to be hospitalized because of drug adverse reactions.

Dose intensity

Dose reduction was not required in any patient because of adverse events. At level 1, treatment had to be delayed for at least 1 week one time during five cycles in 3 of 6 patients, and 1 patient with DLT could not receive chemotherapy on day 8 of cycle 1. The total number of delayed cycles was 3 of 16 (19%). At level 2, treatment had to be delayed for 1 week at least one time in 9 of the 13 patients who received up to five cycles of chemotherapy, and 1 patient did not receive treatment on day 8 of cycle 5 because of fatigue. The total number of delayed cycles was 17 of 62 (27%). During five cycles at level 1, the mean dose intensities (DIs) of 5-FU and irinotecan were 242 mg/m^2 per week and 61 mg/m^2 per week, respectively. The relative DI was 91% of the initial dose for both drugs. During the first five cycles at level 2, the mean DIs of 5-FU and irinotecan were 287 mg/m^2 per week and 62 mg/m^2 per week, and the relative DIs at level 2 were 86% and 93%, respectively.

Table 3. Nonhematologic toxicity in the first two cycles

	Grade 1	Grade 2	Grade 3, 4
Level 1 (n = 6)			
Anorexia	4	0	0
Nausea	1	0	0
Vomiting	0	0	0
Diarrhea	1	1	0
Stomatitis	1	0	0
Fatigue	4	0	0
Level 2 (n = 14)			
Anorexia	8	2	0
Nausea	10	1	0
Vomiting	1	0	0
Diarrhea	3	1	0
Stomatitis	2	0	0
Fatigue	10	0	0

Table 4. Toxicity in all 75 cycles

	Grade 3	Grade 4	All grades (%)
Anorexia	0	0	24 (32)
Nausea	0	0	22 (29)
Vomiting	0	0	4 (5)
Diarrhea	0	0	18 (24)
Stomatitis	0	0	8 (11)
Fatigue	0	0	45 (60)
Febrile neutropenia	1	0	2 (3)
Leukopenia	2	0	35 (47)
Neutropenia	6	1	42 (56)
Hemoglobin decrease	0	0	61 (81)
Thrombocytopenia	0	0	0 (0)
Elevation of AST	0	0	1 (1)
Elevation of ALT	0	0	1 (1)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

Efficacy

Response rates are shown in Table 5. Response was evaluated in 19 of 20 patients (excluding 1 patient in whom the tumor was not assessed after treatment, because of transfer to another hospital before evaluation of response). Two of 6 patients had a partial response at level 1 (33%). At level 2, 9 of 13 patients (69%) responded to treatment. The overall response rate was 58%. As of the time of this writing, all patients who received level 1, and 8 of the 13 patients who received level 2 had disease progression. The median TTP at the RD was 7.8 months.

Discussion

Irinotecan with 5-FU and LV has been shown to be effective for metastatic colorectal cancer in large randomized phase III trials.[5] This three-drug regimen is considered first-line treatment in western countries. However, toxicity associated with the original Saltz regimen (recommending treatment on days 1, 8, 15, and 22 every 6 weeks) often requires dosage modifications to decrease dose intensity.

Treatment for metastatic colorectal cancer must be safe and provide adequate tumor control. We therefore performed a phase I/II study to evaluate the safety and efficacy of a modified Saltz regimen and to confirm starting dose levels for Japanese patients with colorectal cancer. The MTD was not reached because the maximum approved weekly dose of irinotecan in Japan is 100 mg/m^2. We estimated level 2 (irinotecan 100 mg/m^2 with 5-FU 500 mg/m^2 and *l*-LV 10 mg/m^2) to be the RD. In practice, the administered weekly dose of irinotecan may slightly exceed 100 mg/m^2 in some patients given our RD. However,

Table 5. Response rates

	CR	PR	SD	PD	NE	Confirmed response rate
Overall (n = 19)	0	11	3	4	1	58%
Level 1 (n = 6)	0	2	1	3	0	33%
Level 2 (n = 13)	0	9	2	1	1	69%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated

125 mg/m^2 or 150 mg/m^2 of irinotecan weekly would probably result in decreased dose intensity due to severe adverse events. Therefore, we firmly believe that our RD is adequate for Japanese patients.

In our study, only one patient had grade 3 febrile neutropenia as the DLT. This patient had a slightly abnormal bilirubin level 1 week before study entry. The investigator in charge enrolled this patient because the serum bilirubin level had returned to normal at the time of entry. Knight et al.[9] analyzed predictors of toxicity in patients given the original Saltz regimen. Their logistic regression analysis showed that only an elevated bilirubin level predicted a higher incidence of grade 4 neutropenia ($P = 0.03$). They concluded that dose attenuation was most rapid in patients with performance status 2 and abnormal baseline bilirubin. In patients with mildly elevated bilirubin levels, systemic exposure to irinotecan and SN-38 increases the levels considerably, because the pharmacokinetics of irinotecan depend on liver function; dose reduction is therefore required.[12,13] Wasserman et al.[14] reported that patients with Gilbert's syndrome were at increased risk for irinotecan-related toxicity because of deficient UGT*1.1 activity. We recommend that treatment with irinotecan is started at a dose of 100 mg/m^2 in patients with good performance status and normal bilirubin levels. The dose should be reduced in patients with abnormal bilirubin levels.

The most common toxic effect in our study was fatigue, reported in 45 of 75 cycles in eligible patients receiving up to five cycles each. Although not severe, fatigue was a major cause of delayed treatment and occurred frequently after three cycles of chemotherapy. When required, treatment was discontinued for at least 1 week in patients with fatigue. This rest led to recovery in nearly all patients. Postponement of subsequent cycles of chemotherapy also promoted recovery from nausea and anorexia, two other common toxic effects. Neutropenia was another important reason for delaying treatment, and occurred in 42 of 75 cycles, including 7 with grade 3/4 neutropenia. Excluding the patient with DLT, neutropenia usually did not resolve after 1 week of rest. At the RD, the mean absolute DIs of 5-FU and irinotecan were 287 mg/m^2 per week and 62 mg/m^2 per week, and the relative DIs were 86% and 93%, respectively. Differences between the scheduled and administered doses were caused by temporary discontinuation of treatment and dose reduction. On the basis of our experience, we recommend that treatment be suspended for at least 1 week in patients with adverse events.

Our regimen was highly active, with a response rate of 69% in patients receiving the RD. Our overall response rate of 58% is similar to that in previous studies of irinotecan with 5-FU and LV. We conclude that a combination of irinotecan, 5-FU, and *l*-LV is safe, effective, and clinically feasible, and this regimen could be one of the standard first-line treatments for metastatic colorectal cancer in Japan.

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