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Long-Term Survivors of Metastatic Colorectal Cancer Treated with Systemic Chemotherapy Alone: A North Central Cancer Treatment Group Review of 3811 Patients, N0144

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Abstract

Background—Although systemic chemotherapy in patients with unresectable metastatic colorectal cancer (mCRC) is palliative in nature, some patients experience long-term remission beyond 5 years consequent to treatment with chemotherapy alone.

Patients and Methods—We reviewed clinical data from 32 prospective North Central Cancer Treatment Group chemotherapy trials in mCRC that enrolled patients from 1972 to 1995. Metastatic CRC was verified histologically. Excluded from analyses were patients who withdrew consent to the study, enrolled in > 1 study, were ineligible, or had major protocol violations. We defined patients with survival beyond 5 years from the initiation of systemic treatment of mCRC as long-term survivors (LTS).

Results—A total of 36 of 3407 (1.1%) patients were LTS. A total of 13 patients (0.4%) are without evidence of disease or disease progression > 5 years from cessation of last chemotherapy, with a median follow-up of 10.6 years (minimum, 7.6 years). Long-term survivors were more likely to have received 5-fluorouracil (5-FU)-based treatment (33 of 2503 [1.3%]) as opposed to other, less effective therapy (3 of 904 [0.3%]), suggesting that the chemotherapy played an important role among LTS ($P = .01$). Clinical characteristics of LTS were similar to the overall population in terms of age, sex, performance status, and tumor grade.

Conclusion—This study establishes a baseline for long-term outcomes of mCRC in the era when effective treatment was limited to 5-FU. With the development of improved systemic therapy for mCRC, cure without salvage surgery might be possible for a small, but important number of patients. Clinical trials should follow patients for > 5 years to document the long-term outcomes.

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Disclosures

The authors have no relevant financial relationships to disclose.

Keywords

5-Fluorouracil; Disease site; Leucovorin; Liver metastasis

Introduction

Metastatic colorectal cancer (mCRC) is the second leading cause of cancer death in the United States. Randomized trials of best supportive care versus chemotherapy have established the benefit of cytotoxic treatment in terms of survival and quality of life.^{1–4} First-line chemotherapy with 5-fluorouracil (5-FU)-based regimens is considered standard practice. Before the introduction of oxaliplatin, irinotecan, and other novel molecularly targeted signal transduction inhibitors, median survival was 12–15 months from the time of diagnosis of metastasis.^{5,6} Long-term survival in mCRC can be achieved in a minority of patients with a multimodal treatment approach, particularly when all known disease sites are resected.^{7–15} There are little data whether long-term survival with systemic chemotherapy alone is observed. Most of the reports in the literature regarding this subject are anecdotal or short case series. Massacesi et al have published a nomogram using clinical information collected prospectively from 1057 patients with advanced CRC to predict for long-term survival.¹⁵ However, their study was limited by several factors. The median follow-up duration (38 months) and the definition of long-term survival as > 2 years were inadequate to distinguish patients who have indolent disease from, and to restrict analysis to, patients who are truly long-term survivors (LTS) as a result of systemic therapy alone. Moreover, long-term survival has conventionally been defined (somewhat arbitrarily) by at least 5-year survival rates after cancer diagnosis.¹⁶ Colorectal cancer has a variable course, and in some patients, the ‘natural course of disease’ metric of 5-year survival cannot be used as a surrogate for ‘cure’ rate.^{17,18} Moreover, Massacesi et al included patients who underwent surgery and radiation therapy for curative intent of metastases. Perez et al included 5-year and 10-year long-term outcomes in their recent report; however, their study likewise included patients who underwent surgical resection for metastatic disease.¹⁹

Long-term survival rates are widely used outcome measures for cancer patients to monitor progress in cancer care over time. We thus undertook this study to determine the frequency and clinical characteristics of patients with mCRC who had long-term survival > 5 years after treatment with pre-1995 systemic chemotherapy alone. This information will be useful for subsequent studies on the changes in the trends of survival outcomes with newer regimens. Moreover, the ability to identify this group of patients might help direct treatment decisions that will minimize morbidity and unnecessary interventions from a multimodality approach.

Patients and Methods

Patients

Institutional review board approval was granted before conducting this study. We reviewed the database established for all phase II and III chemotherapy trials for mCRC conducted by the North Central Cancer Treatment Group (NCCTG) from the mid-1970s to the early 1990s to identify LTS. We defined LTS as patients who are alive > 5 years after initial treatment of mCRC, without the benefit of surgical resection. Patients must have been eligible for and treated on at least one of the aforementioned NCCTG mCRC chemotherapy trials. Baseline laboratory and pathology reports, performance status (PS), treatment duration, treatment response, disease-free interval, and survival data are contained in these records. All patients had histologic or cytologic confirmation of mCRC. However, protocols do not mandate that all anatomic sites of metastases require pathologic confirmation. Patient study records were

individually reviewed for each LTS to confirm survival and determine whether surgery was performed for mCRC.

Staging and measurement of disease was by computed tomography (CT) scan and, if appropriate, other radiologic investigations or endoscopy. Patients' PS was graded according to the Eastern Cooperative Oncology Group scale and recorded at the initial consultation. Response to systemic therapy was classified using the World Health Organization objective response criteria.

Chemotherapy

The various chemotherapy regimens used in the 32 prospective phase II and III NCCTG chemotherapy trials for mCRC, both first-line and subsequent therapies, included in this analysis are shown in Table 1.

Statistics

Overall survival (OS) was defined as the time from study registration to death from any cause. Because of the variety of treatments used, and that only a small number of LTS were identified, this study is primarily descriptive in nature. Univariate association between LTS status and baseline demographics were performed using a *t* test for age and duration of therapy and Fisher exact test for categorical covariates, with $P < .05$ used to denote statistical significance.

Results

Demographics

There were 3811 patients treated on 32 NCCTG clinical trials for mCRC. A total of 396 patients either withdrew consent to the study, enrolled in > 1 study, were ineligible, or had major violations and were removed from further analysis. Eight LTS patients had surgical resection of mCRC and were also excluded. Of the remaining 3407 patients, 2503 patients were treated with 5-FU-based regimens; 904 patients received other chemotherapy. Median follow-up for living patients was 9.9 years.

Of the 3407 patients, 3403 (99.9%) were followed until their demise or for > 5 years. Figure 1 presents the Kaplan-Meier estimate of OS; Table 2 presents the estimated survival rate by year. Thirty-six patients (1.1%) survived > 5 years with chemotherapy alone. Thirteen patients (0.4%) had no evident site of disease involvement for > 5 years from last treatment. Nineteen of the 36 patients (53%) received at least two lines of chemotherapy, to a maximum of 3 salvage regimens. Five of the 36 patients (14%) developed a metachronous colorectal malignancy > 12 months from initial diagnosis of colon cancer, one of which was diagnosed while the patient was receiving systemic therapy. Characteristics of LTS are shown in Table 3.

A total of 19 deaths were documented at the last follow-up among the 36 LTS. A total of 14 patients and 3 patients died of mCRC between 5–8 years and between 8–10 years of follow-up, respectively. One patient died of a cerebrovascular event 9 years after her initial diagnosis of metastatic disease. She had been off systemic cancer therapy for approximately 3 years before her demise. Another patient was off treatment and deemed to have no evident site of disease involvement (NED) for 19 years before her death, which occurred 23 years after the diagnosis of mCRC. The cause of this patient's death was unknown.

A total of 13 patients were without evidence of disease > 5 years from cessation of last chemotherapy until death or the last follow-up (range, 7.6–23 years).

Comparison of Long-Term Survivors with Control Patients with Metastatic Colorectal Cancer

The relationship between LTS status and patient characteristics was examined on the subset of patients treated on the five largest trials where the variables of interest were consistently collected; this included 35 of the 36 LTS (Table 3). Mean age, PS, sex, primary tumor location, and tumor grade did not differ significantly among patients with LTS from the general treatment mCRC population/ control population.

Effect of Chemotherapeutic Agent

A total of 33 patients (1.3%) were LTS among the 2503 patients treated with 5-FU based regimens. Three patients (0.3%) were LTS among the 904 patients treated with other non-5-FU-based regimens. Patients receiving 5-FU-based regimens were more likely to be LTS ($P = .01$). Twelve of 13 patients deemed to have NED status received 5-FU-based therapy.

Discussion

We performed a review of data from 32 clinical trials in mCRC enrolling 3811 patients to identify the subset of patients with long-term survival > 5 years from initiation of therapy for their advanced disease. To our knowledge, this study presents the largest group of LTS with the longest follow-up data among patients with mCRC treated with systemic chemotherapy alone. Because all patients had clinically evident biopsy-proven metastases and PET scans were not incorporated in the staging of disease, our observations were not likely to be subject to stage migration bias.

Although the median survival of patients with mCRC was approximately 1 year using pre-1995 chemotherapy regimens, in our experience approximately 1.1% have an unusually long survival after diagnosis and treatment with systemic chemotherapy alone; rarely, the disease appears to be “cured.” The clinical characteristics of the group of LTS do not readily explain why most patients with mCRC who have a similar constellation of features die faster than LTS. The use of 5-FU-based regimen was independently associated with LTS. In fact, with the availability of newer drugs such as oxaliplatin, preliminary evidence suggests that the ability of systemic treatment alone to attain complete tumor responses in mCRC can result in durable survival outcomes comparable to those seen among patients who undergo additional locoregional therapies such as surgical resection of residual operable metastases.²⁰

The phenomenon of LTS among patients with mCRC is not widely appreciated because 5-year survival rate among patients with distant metastases is approximately 1%. However, the fact that patients with mCRC can survive in the ‘long tail’ of the survival distribution attests to the underlying heterogeneity of tumor behavior and response to treatment. Although rapidly-growing CRC has been reported, tumor growth of CRC in terms of tumor volume doubling time is characteristically deemed slow in relation to other tumors.^{17,21} Patients with metastatic disease have been reported to live for > 5 to 10 years, without any specific therapy.^{22,23} Indeed, our own study showed that half of the patients who were LTS could not be considered ‘cured’ of their disease because they ultimately died from cancer. However, the remaining half of the group of LTS apparently may be considered cured because the majority do not have any evident site of metastatic involvement after therapy. The concept of conditional survival on prognosis might thus be applicable for LTS among patients with metastatic disease, albeit in a limited sense, as it does for earlier stages of CRC.²⁴ Similar observations of long-term survival have been reported in patients with metastatic breast cancer.^{25–28} A limitation inherent in this study lies in the variability/ reproducibility in the determination of tumor response evaluation in the clinical setting,²⁹

which partly resides in the ‘overclassification’ of imaging abnormalities as metastatic disease when they are in fact nonmalignant. Another limitation in this study is that inherent tumor biology is unknown; thus, the contribution of this variable to treatment-associated long-term survival cannot be established and is a potential confounding factor,³⁰ and an imbalance of favorable prognostic markers up front might have skewed the clinical course of patients that led to our observation of more LTS in patients receiving 5-FU than non-5-FU therapies. Hence, the importance of tissue banking in conjunction with large phase III trials cannot be overemphasized as technological improvements in molecular analyses of banked specimen will allow us to longitudinally study and identify prognostic features associated LTS separate from predictive markers of treatment response. Ultimately, long-term survival is the result of effective therapy as well as favorable intrinsic tumor biology, and research endeavors should continue to improve the former and understand the latter.

Conclusion

In the 5-FU era, approximately 1.1% of patients with histologically confirmed, unresected mCRC survived 5 years after initiation of chemotherapy. Approximately 1 of every 200 patients appear to have been potentially cured of mCRC by systemic chemotherapy alone. Long-term survivors were similar to the general treatment mCRC population with respect to age, PS, sex, tumor grade, and sites of metastatic disease. Treatment with a 5-FU-based regimen was an important determinant in the outcome among patients with LTS. Future clinical trials of chemotherapy of mCRC should track the frequency of LTS to determine the number of patients who are LTS with newer therapies. Further investigations are needed to characterize the distinct molecular features of LTS, knowledge of which will be of vital interest in treatment decision-making and in endeavors to improve ‘tailored’ therapies appropriate to individual patients.

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Figure 1.
Kaplan-Meier Estimate of Overall Survival

Table 1

List of Protocols and Patient Enrollment Included in This Analysis

Protocol Number	Chemotherapy Agents	Number of Patients	Number of Patients Who Lived > 5 Years	Number of Patients Alive at Last Follow-up
701801	Methyl CCNU, 5-FU, and ifosfamide	76	1	0
701831	(A) 5-FU, doxorubicin; (B) 5-FU, vincristine, and methyl CCNU	109	0	0
701833	(A) Combined 5-FU, methyl CCNU, and vincristine; (B) 5-FU and methyl CCNU; (C) 5-FU and CAC platinum with a controlled evaluation of MER as an adjuvant immunostimulant	158	1*	0
754601	VP-16 (NSC-141540) and galactitol (NSC-132313)	59	0	0
754604	Triazinate (TZT, Baker's Antifol)	29	0	0
764601	Pyrazofurin (PRZF)	37	0	0
764602	Cytosine arabinoside (Ara-C)	32	1*	0
764802	(A) Tegafur; (B) 5-FU, methyl CCNU and TZT; (C) 5-FU, methyl CCNU, and ICRF-159; (D) 5-FU, methyl CCNU	202	0	0
774601	Maytansine	31	0	0
774603	Hycanthone (NSC-14982)	30	0	0
784601	Cyclophosphamide, doxorubicin, and cis-platinum	30	0	0
784602	Chlorozotocin	66	0	0
784651	(A) 5-FU plus TZT; (B) 5-FU plus ICRF-159; (C) methyl CCNU plus ICRF-159; (D) methyl CCNU plus TZT; (E) ICRF-159 plus TZT; (F) 5-FU alone	248	0	0
794601	Indicine-N-Oxide (NSC 132319)	30	0	0
794602	N-(Phosphonacetyl)-L-Aspartate (PALA)	31	0	0
794605	6-Thioguanine	31	0	0
804601	L-Alanosine	30	0	0
804602	Aziridinybenzoquinone (AZQ; NSC 182986)	31	0	0
804605	6-Diazo-5-Oxo-L-Norleucine (DON, NSC-7365)	30	0	0
804606	9-10 Anthracenedicarboxaldehyde bis (4,5-dihydro-1H imidazol-2-yl) hydrazone dihydrochloride (CL216,942; ADAH)	31		0
804651	(A) 5-FU; (B) 5-FU plus TDR; (C) 5-FU plus PALA; (D) 5-FU plus LV; (E) 5-FU plus methyl CCNU plus vincristine plus streptozotocin	347	5	1
814602	BCNU and PALA	30	0	0
814603	PALA (NSC-224131) and L-Alanosine (NSC-153353)	31	0	0
824601	PALA/5-FU/Thymidine	44	0	0
834601	High-dose cis-platinum in combination with loading course 5-FU	33	0	0
834652	(A) 5-FU plus methotrexate; (B) 5-FU plus LV (high dose); (C) 5-FU plus LV	703	12	5
844601	Tricyclic Nucleoside 5'-Phosphate (NSC 280594)	31	0	0
854601	Recombinant human interferon- γ	36	0	0
874601	Intravenous 6-Thioguanine	15	0	0
874652	Somatostatin	263	4	2

Protocol Number	Chemotherapy Agents	Number of Patients	Number of Patients Who Lived > 5 Years	Number of Patients Alive at Last Follow-up
894652	(A) 5-FU plus the l-isomer of LV; (B) 5-FU plus oral (d,l) LV; (C) 5-FU plus intravenous (d,l) LV	942	21	8
904601	5-FU and levamisole	15	0	0

* Same patient, enrolled to studies sequentially after disease progression.

Abbreviations: 5-FU = 5-fluorouracil; LV = leucovorin

Table 2

Estimated Survival Rate by Year

Year Number	Estimated Survival	95% CI
1	0.373	0.358–0.390
2	0.124	0.114–0.136
3	0.045	0.038–0.052
4	0.018	0.014–0.023
5	0.011	0.008–0.015
6	0.008	0.006–0.012
7	0.007	0.004–0.010
8	0.007	0.004–0.010
9	0.006	0.004–0.009
10	0.005	0.003–0.008

Table 3

Characteristics of Long-Term Survivors*

Characteristic	Non-LTS (N = 2334)	Patients Surviving > 5 Years (N = 35)	P Value Comparing Non-LTS to LTS	NED at Last Evaluation (N = 12)
Age, Years				
Mean	63	62	.7037	59
Median	64	65	–	65
Range	14–90	32–80	–	32–74
Sex (%)				
Female	1029 (44)	11 (31)	.1696	6 (50)
Male	1305 (56)	24 (69)	–	6 (50)
Disease Grade (%)				
1–2	1646 (71)	22 (63)	.2538	6 (50)
3–4	633 (27)	13 (37)	–	6 (50)
Missing	55 (2)	–	–	–
Performance Score (%)				
0	861 (37)	18 (51)	.2377	6 (50)
1	1093 (47)	13 (37)	–	3 (25)
2–3	379 (16)	4 (11)	–	3 (25)
Missing	1 (0)	–	–	–
Primary Site (%)				
Left	929 (40)	16 (46)	.1595	1 (8)
Right	760 (33)	12 (34)	–	7 (58)
Rectal	399 (17)	7 (20)	–	4 (33)
Other	246 (11) [†]	–	–	–
Metastatic Site[‡]				
Liver	–	17	–	7
Lung	–	6	–	2
Lymph node	–	6	–	1
Intra-abdominal	–	12	–	5
Pelvis	–	3	–	1
Response (%)				
CR	31 (1)	7 (20)	< .0001	5 (42)
PR	292 (13)	3 (9)	–	1 (8)
SD	1657 (71)	25 (71)	–	6 (50)
PD	302 (13)	–	–	–
Unknown	52 (2)	–	–	–
Duration of Treatment, Days				
Mean	154	855	< .0001	1058
Median	92	552	–	634

Characteristic	Non-LTS (N = 2334)	Patients Surviving > 5 Years (N = 35)	P Value Comparing Non-LTS to LTS	NED at Last Evaluation (N = 12)
Range	1–1611	1–3153	–	1–2915

* Studies 784651, 804651, 834652, 874652, 894652.

[†] Contains colon not otherwise specified (239), intestinal (1), cervix (2), and ovary (4).

[‡] Metastatic site information from chart reviews; and this was not performed for non-LTS patients.

Abbreviations: CR = complete response; LTS = long-term survivors; NED = no evident site of disease involvement; PD = progressive disease; SD = stable disease