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Preliminary results of metabolically supported chemotherapy combined with ketogenic diet, hyperthermia and hyperbaric oxygen therapy in stage II-IV rectal cancer

Evre II-IV rektum kanserinde metabolik destekli kemoterapinin ketojenik diyet, hipertermi ve hiperbarik oksijen tedavisi ile kombinasyonunun ön sonuçları

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Abstract

Aim: Systemic chemotherapy is a part of multi-modality treatment in patients with stage II-IV rectal cancer. In particular, patients not eligible for curative resection at the time of diagnosis require more efficient approaches to improve outcomes. Metabolically supported chemotherapy (MSCT) is a novel approach targeting dysregulated energy mechanism of the tumor cell. This study aimed to examine the efficacy of MSCT combined with ketogenic diet, hyperthermia and hyperbaric oxygen therapy (HBOT) in patients with stage II-IV rectal cancer not eligible for surgery at baseline.

Methods: Twenty-one patients diagnosed with stage II-IV rectal carcinoma who received metabolically supported chemotherapy (MSCT) combined with ketogenic diet, hyperthermia and HBOT were included. First-line chemotherapy regimen was oxaliplatin-based, whereas second line regimen was irinotecan-based. Overall survival and progression-free survival were estimated.

Results: Mean duration of follow-up was 33.3±22.0 months. Mean overall survival was 58.6 months (95% CI, 43.3 - 73.9) and corresponding figure for progression-free survival was 45.1 months (95% CI, 28.9-61.2). Mean overall survival for patients with metastatic disease was 35.7 months. Multivariate analysis identified male gender and stage IV disease as independent predictors of worse progression free survival. No other parameter effected survival outcomes.

Conclusion: Findings of this study are promising for potential use of this novel combinatorial protocol targeting multiple vulnerabilities of tumor cells in patients with advanced rectal cancer, particularly for patients with metastatic disease, without additional safety concerns. However, long term results are warranted to draw firm conclusion.

Key words: rectal cancer, metabolically supported chemotherapy, ketogenic diet, hyperthermia, hyperbaric oxygen therapy, survival

Öz

Amaç: Evre II-IV rektum kanserinde sistemik kemoterapi multimodalite tedavisinin bir parçasıdır. Özellikle, tanı sırasında küratif rezeksiyona uygun olmayan hastaların sonuçlarını iyileştirmek için daha etkili yaklaşımlara gerek vardır. Metabolik destekli kemoterapi (MDKT) tümör hücresinin bozulmuş enerji metabolizmasını hedef alan yeni bir yaklaşımdır. Bu çalışma, ketojenik diyet, hipertermi ve hiperbarik oksiyen tedavisi (HBOT) ile kombine edilmiş MDKT'nin başlangıçta cerrahi için uygun olmayan evre II-IV rektum kanseri hastalarındaki etkinliğini değerlendirmeyi amaçlamıştır.

Yöntemler: Metabolik destekli kemoterapi (MDKT) tedavisi ile ketojenik diyet, hipertermi ve HBOT kombinasyonu almış 21 evre II-IV rektum kanseri hastası çalışmaya dahil edilmiştir. Birinci basamak kemoterapi oksaliplatin bazlı, ikinci basamak kemoterapi ise irinotekan bazlıdır. Genel sağkalım ve progresyonsuz sağkalım hesaplanmıştır.

Bulgular: Ortalama takip süresi 33.3±22.0 aydır. Ortalama genel sağkalım 58.6 ay (95% CI, 43.3 - 73.9), ortalama progresyonsuz sağkalım 45.1 ay (95% CI, 28.9-61.2) olarak bulunmuştur. Metastatik hastalığı olanlarda ortalama genel sağkalım 35.7 ay olmuştur. Çok değişkenli analiz erkek cinsiyet ve evre IV hastalığın kötü progresyonsuz sağkalım için bağımsız belirteçler olduğunu göstermiştir. Başka hiçbir parametre sağkalım sonuçlarını etkilememiştir.

Sonuç: Bu çalışmanın bulguları, tümör hücresinin birçok zayıf noktasını hedef alan bu yeni kombinasyon protokolünün ilerlemiş rektum kanseri hastalarında, özellikle de metastatik hastalığı olanlarda, ek güvenilirlik endişesi oluşturmadan kullanılabileceği yönünde ümit vermektedir. Ancak, daha net çıkarımlara ulaşmak için uzun dönem sonuçlar gereklidir.

Anahtar Kelimeler: rektum kanseri, metabolik destekli kemoterapi, ketojenik diyet, hipertermi, hiperbarik oksijen tedavisi, sağkalım

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Introduction

Colorectal cancer represents an important cause of mortality and morbidity. In the US, it is the second leading cause of cancer related deaths and the fourth most frequently diagnosed malignancy [1]. However, last decades witnessed substantial decreases in its incidence and mortality [2-4], most probably owing to screening resulting in early detection and prevention, and advances in treatment modalities.

Recent guidelines recommend combined-modalities consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoRT), and chemotherapy for most patients with stage II or III rectal cancer [1]. Several regimens including FOLFOX and FORFIRI have been examined for systemic chemotherapy for metastatic disease [5, 6]. Although encouraging results have been obtained with combination of treatments and advances in modalities, patients who are not eligible for curative resection at the time of diagnosis require more efficient approaches to improve outcome.

Metabolically Supported Chemotherapy (MSCT) is a novel chemotherapy application strategy targeting metabolic vulnerabilities of cancer cells [7-10]. Cancer cells have a dysregulated energy metabolism almost evident in all tumor types [11], which was first recognized by Otto Warburg, in 1924 [12, 13]. Insufficient oxidative phosphorylation is compensated by aerobic fermentation, resulting in glucose dependency and increased lactate production. These abnormalities have been linked to mitochondrial dysfunction and genetic mutations [11, 14, 15]. MSCT targets glucose dependency of tumor cells as well as membrane permeability to chemotherapeutic drugs, which increases by the administration of insulin [16]. It integrates 12-hour fasting and administration of insulin to the usual chemotherapy schedule, thereby reducing the available glucose for the tumor cells. Adopting a ketogenic diet further decreases circulating glucose levels. A high-fat, carbohydrate-restricted ketogenic diet has been shown to slow the progression of cancer [8, 9, 17, 18].

Hyperthermia and hyperbaric oxygen therapy (HBOT) are two modalities that are shown to have additional beneficial contributions to chemotherapy. Hyperthermia causes direct cytotoxicity and acts synergistically with radiotherapy and chemotherapy through sensitizing cancer cells to these therapies [7-10, 19-22]. HBOT on the other hand, results in better oxygenation of tumor cells thus counteracting unfavorable consequences of hypoxia, which has cancer promoting effects and promotes resistance to chemotherapy and radiotherapy [23-27]. To date, several clinical studies demonstrated their benefit when used in combination with chemotherapy and radiotherapy [8-10, 19, 20].

Based on the supporting evidence from the abovementioned studies, MSCT, ketogenic diet, hyperthermia and HBOT have the potential to work together by targeting vulnerabilities of cancer cells and several overlapping metabolic pathways. To date, no study has reported the efficacy of this novel strategy in the treatment of rectal cancer. We hypothesize that this approach would result in encouraging treatment outcomes in rectal cancer patients.

In this study we aimed to evaluate the efficacy of MSCT combined with ketogenic diet, hyperthermia and HBOT in the treatment of stage II-IV rectal cancer patients.

Material and methods

After approval of the ethical committee, the study was conducted according to the principles described in the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Study design and patient selection

Twenty-one patients diagnosed with stage II, III, or IV rectal carcinoma between February 2012 and September 2017 who received MSCT together with ketogenic diet, hyperthermia and hyperbaric oxygen therapy were included in this retrospective single-center study. Patients were either not eligible for or refused to have surgical resection at the time of diagnosis. In addition, patients adapted a ketogenic diet and at each chemotherapy session they received hyperthermia application and hyperbaric oxygen therapy. A prospectively maintained institutional database was screened to identify patients from a subset diagnosed with rectal cancer (any class, stage or subtype) and treated at our clinic with this combinatorial protocol during the study period. Inclusion criteria were as follows: biopsy-proven rectal cancer, measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [28], radiologically-proven staging of disease, and receiving MSCT together with ketogenic diet, hyperthermia and hyperbaric oxygen therapy.

Chemotherapy regimen

All patients received a chemotherapy regimen consisting of oxaliplatin 85 mg/m2 IV over 2 h on day 1 plus leucovorin 400 mg/m2 IV over 2 h on day 1 plus 5-FU 400 mg/m2 IV bolus on day 1, then 5-FU 1200 mg/m2/day for 2 days (total 2400 mg/m2 over 46-48 hours) continuous infusion as first-line treatment. This combination treatment was administered in an outpatient setting and repeated every 2 weeks until disease progression. In case of progression, patients were administered a chemotherapy regimen consisting of irinotecan 180 mg/m2 IV over 30-90 min on day 1 plus leucovorin 400 mg/m2 IV infusion over 30-90 min on day 1 plus 5-FU 400 mg/m2 IV bolus on day 1, then 5-FU 1200 mg/m2/day for 2 days (total 2400 mg/m2 over 46-48 hours) continuous infusion repeated every 2 weeks as second-line treatment. Assessment of treatment response was based on radiographic evaluations at the end of each 3-month period and was always done by PET-CT. Patients that achieved complete response (CR), partial response (PR), or stable disease (SD) status continued to receive maintenance therapy with the same regime until death as far as tolerated.

Administration of metabolically supported chemotherapy

All eligible patients were advised to adapt a ketogenic diet during the study period and they were asked to fast for 12 hours before each chemotherapy session. In addition to the premedication with 45.5 mg pheniramine maleate and 0.25 mg palonosetron HCl, each patient received regular insulin (Humulin® R) in doses ranging between 5-20 IU prior to chemotherapy administration in order to achieve a state of mild hypoglycemia with blood glucose levels around 50-60 mg/dl for normoglycemic patients and in accordance with MSCT protocols [7-10]. Following each MSCT administration, patients received a 60-minute session of hyperthermia and a 60-minute session of

HBOT. Hyperthermia was provided using OncoTherm EHY-3010 HT device (OncoTherm, Troisdorf, Germany). The temperature of the tumoral region was gradually increased to 45°C with a mobile electrode. For HBOT, Quamvis 320 hyperbaric oxygen chamber (OxyHealth, California, US) was used and the patient was subjected to 1.5 atmospheres pressure (ATA).

Statistical analysis

IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL) was used for data analyses. Overall survival was defined as the time between the date of diagnosis and death from any cause. Progression free survival was defined as the time between the date of diagnosis and progression or death from any cause. Patients without event at the last follow up were censored. Survival rates were estimated using Kaplan-Meier analysis, and intergroup comparisons were done with log-rank test. Univariate potential predictors were entered into Cox proportional hazards model to identify independent predictors of survival outcomes. Level of significance was set at <0.05.

Results

Table 1 shows demographical and clinical characteristics of the patients. All patients had adenocarcinoma. Mean duration of follow-up was 33.3±22.0 months (median 28.3, range 8.9-84.0 months). During the follow-up period 7 patients died. Mean overall survival was 58.6 months (95% CI, 43.3 - 73.9) and corresponding figure for progression-free survival was 45.1 months (95% CI, 28.9-61.2). Figure 1 shows Kaplan-Meier curves for overall survival and progression free survival. 1-year and 2-year overall survival rates were 95% and 80%, respectively.

Table 1: Demographical and clinical characteristics of the patients.

Characteristic	n=21
Age, year, median (range)	60 (40-82)
Male gender	11 (52.4%)
Stage	
II	5 (23.8%)
III	10 (47.6%)
IV	6 (28.6%)
Histological grade	
2	16 (76.2%)
3	5 (23.8%)
Surgery*	10 (47.6%)
Radiotherapy	18 (85.7%)

Unless otherwise stated, data presented as n (%)
*These patients received surgical treatment after complete response to chemotherapy.

Table 2 shows overall survival and progression-free survival rates by patient characteristics. None of the patient characteristics have effect on overall survival. However, in univariate analysis, stage IV patients had worse progression-free survival when compared to stage II-III patients (21.2 vs. 51.9 months, p=0.014). In multivariate analysis, patients with stage IV disease (OR, 26.4; 95% CI: 1.5-456.4; p=0.024) and male patients (OR, 33.4; 95% CI: 1.5-744.7; p=0.027) had worse progression-free survival. None of the other patient characteristics effected survival outcomes. Figure 2 shows Kaplan Meier curves for progression free survival by gender and stage.

Table 2: Survival rates by patient characteristics (univariate analysis).

Characteristic	Mean OS (95% CI) (months)	p [a]	Mean PFS (95% CI) (months)	p [a]
All patients (n=21)	58.6 (43.3 - 73.9)		45.1 (28.9-61.2)	
Age				
≤ median (n=12)	63.8 (43.3 - 84.3)	0.392	41.5 (20.6-62.3)	0.355
> median (n=9)	47.5 (28.1-66.9)		50.6 (30.9-70.3)	
Gender				
Male (n=11)	56.2 (38.0-74.3)	0.798	27.7 (16.8-38.6)	0.124
Female (n=10)	56.8 (38.9-74.6)		53.7 (33.7-73.6)	
Stage				
II-III (n=15)	63.3 (46.5-80.2)	0.255	51.9 (33.2-70.7)	0.014
IV (n=6)	35.7 (27.9-43.5)		21.2 (13.1-29.3)	
Histological grade				
2 (n=16)	60.6 (52.3-69.0)	0.333	47.0 (34.0-60.0)	0.356
3 (n=5)	50.3 (22.1-78.5)		36.6 (13.7-59.6)	
Surgery				
Surgery added (n=10)	56.8 (34.8-78.7)	0.897	34.2 (15.1-53.3)	0.201
No surgery(n=11)	53.2 (33.3-73.2)		51.8 (34.4-69.2)	
Radiotherapy				
Radiotherapy added (n=18)	59.6 (9.9-40.3)	0.780	51.6 (31.4-71.7)	0.070
No radiotherapy (n=3)	53.0 (32.6-73.4)		26.7 (12.8-40.7)	

[a]Log-rank test. OS, overall survival; PFS, progression-free survival.

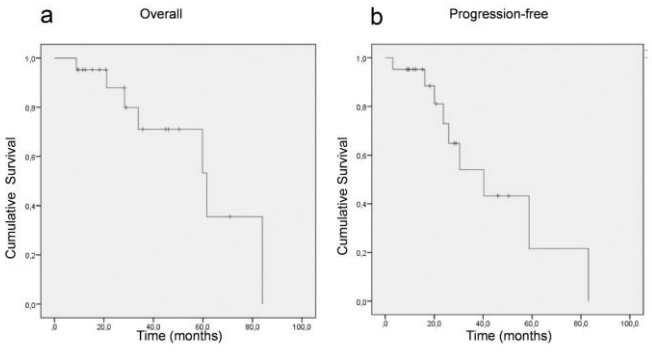

Figure 1: Kaplan Meier curves for overall survival (a) and progression free survival (b) in all patients.

During the study period, no significant or severe problems were encountered due to fasting, hypoglycemia, hyperthermia or hyperbaric oxygen therapy. However, mild

burning sensation at the site of hyperthermia application and mild earache immediately after hyperbaric oxygen therapy were rarely reported by some patients. Both were self-limiting and lasted not more than a couple of hours in all cases.

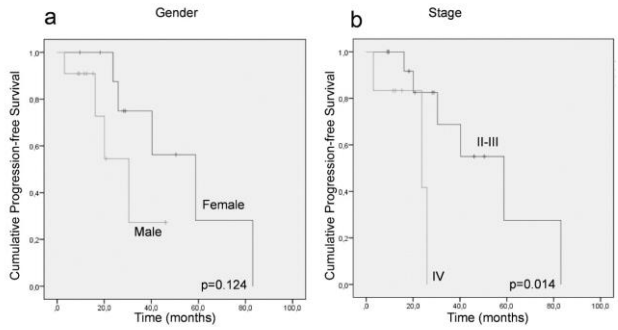

Figure 2: Kaplan Meier curves for progression-free survival by gender (a) and stage (b). P values are calculated with Log rank test.

Discussion

This is the first study to examine the combination of MSCT with ketogenic diet, hyperthermia and HBOT in rectal cancer, and findings are promising in terms of survival outcomes, particularly for the patients with metastatic disease. This novel combination treatment targets multiple susceptibilities of the tumor cell; at metabolic, cellular and pharmacological levels.

In patients with stage II and III rectal cancer who underwent preoperative chemotherapy, reported long-term overall survival rates are usually over 60% [29-31]. In this study, we administered a novel combination of MSCT with ketogenic diet, hyperthermia and HBOT and achieved promising 1- and 2-year overall survival rates of 95 and 80% in a heterogenous group of stage II-IV patients who were not eligible for surgery at baseline; however, since the follow-up period is not long enough to reach median survival, it does not seem plausible to give reliable 5- and 10-year overall survival rates. On the other hand, mean overall survival rate among the patients with metastatic disease achieved in this study is 35.7 moths, which is relatively long for such group of patients with an unfavorable outlook. For example, a recent study included rectal carcinoma patients with synchronous metastases who received combination of FOLFOX chemotherapy with split-course pelvic chemoradiation (FOLFOX + CRT) and obtained median overall survival of 23 months [32]. Another study compared outcomes of neoadjuvant chemoradiotherapy and postoperative systemic chemotherapy without radiotherapy in metastatic rectal cancer patients and achieved 24 and 27 months of median overall survival, respectively [33].

Clinical evidence on the potential benefit of MSCT comes from clinical studies with pancreatic cancer patients and non-small cell lung cancer patients as well as from two case reports. In a recent study with stage IV ductal pancreatic adenocarcinoma patients, metabolically supported administration of chemotherapy resulted in promising survival outcomes with a reported median survival of 15.8 months [9]. Another recent study reported encouraging results in stage IV non-small cell lung cancer with a mean 42.9 months overall survival rate [10]. In addition, good responses have been reported in an 81-year old patient with locally advanced rectal cancer and a stage IV triple negative breast cancer patient when chemotherapy regimen was administered in a metabolically supported form [7, 8]. Several mechanisms may play role in the favorable contribution of metabolic support to treatment efficacy. Induced hypoglycemia is the main consequence of metabolic support through fasting and insulin administration. Due to dysregulated energy metabolism, cancer cells are more dependent on circulating glucose, thus scarcity of available glucose will pose an acute metabolic stress on these cells, especially when compared to healthy cells, which will render them more susceptible to the cytotoxic effects of chemotherapy [11-15]. In addition, insulin has the potential to increase membrane fluidity and permeability [34, 35]. Internalization of drug-insulin complexes through receptor mediated endocytosis would ensure rapid transfer into the cell, thereby enhancing cytotoxic effects [36, 37]. The density of insulin and insulin-like growth factor (IGF) receptors is higher on tumor cells when compared to their healthy counterparts [38, 39]. The reaction between insulin and these receptors would extend the S-phase of the cell cycle and render them more susceptible to the cytotoxic effects of chemotherapeutics for longer periods [40]. On the other hand, lower density of these receptors on healthy cells would relatively protect them from the cytotoxic effects of chemotherapeutic drugs, which may translate into less adverse effects.

Ketogenic diet has been used for decades as a treatment for intractable pediatric epilepsy; however, its possible use in cancer therapy has recently been explored. Similar to fasting and insulin administration in conjunction with chemotherapy, adapting a ketogenic diet also targets the increased glucose dependency of the cancer cell. Several studies provided evidence for its potential role in the treatment of cancer [8, 17, 18, 41-45]. Hyperthermia itself is cytotoxic. HBOT also targets the reliance of tumor cells on glycolysis, a major contributor to the upregulation of antioxidant activity responsible for the increased resistance of the tumor to pro-oxidant chemotherapy and radiation therapies [46]. Concomitant use of these therapies and potential synergism between them have been explored in previous studies [8, 11, 18-21, 27, 41, 47, 48]. For example, Ohguri et. al. obtained promising results in NSCLC patients with multiple pulmonary metastases in association with the concomitant administration of carboplatin/paclitaxel chemotherapy regimen, hyperthermia and HBOT [19].

Retrospective design, small sample size, patient heterogenicity and short follow-up are the major limitations of this study. Low sample size might have resulted in low statistical power not sufficient to detect survival differences between risk groups. Due to short follow-up, median survival could not be reached, and long-term survival rates cannot be estimated. Nevertheless, findings of this study underscore the potential benefits of exploring and integrating additional modalities targeting cellular vulnerabilities of the cancer cell to conventional chemotherapy, provided that they are based on biochemical and pharmacological rationale.

In conclusion, our findings suggest that MSCT combined with a ketogenic diet, hyperthermia and HBOT appears to be a feasible approach for the treatment of patients with advanced rectal cancer or in patients that surgical treatment is not feasible. Further research, especially comparative clinical trials with long-term follow-up are warranted to support this protocol.

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