August 20, 2014

Margaret Obermeyer
Investigations and Resolutions
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Dear Ms. Obermeyer,

I, , am a duly licensed physician in the province of Ontario. I am currently a staff medical oncologist at the where I have practiced for the past years. Prior to I was a staff medical oncologist at the . where I completed my subspecialty training in Hematology/Oncology. I am an Assistant Professor in the division of Medical Oncology in the Department of Medicine at
My clinical practice is limited to the treatment of gastrointestinal malignancies, of which colorectal cancer accounts for the majority of cases.

I have been asked to review the case of Georgia Karamitos who was treated by Dr. Akbar Khan and to determine if Dr. Khan has maintained the standards of practice in the given circumstances. My report is based on the review of the files provided to me including the letter of complaint from Dr. Trinkaus, printouts of the webpages from Berkely Institute International webpages, ALIN foundation, Medicor Cancer Centre, the response from Dr. Khan, the letter from Dr. Matsumura to Dr. Khan, the comments from Dr. Trinkaus received May 13, 2014, the letter from Ms. Constantine and the patient's records from the Medicor clinic. My report will review the clinical course of this patient with metastatic colorectal cancer and will detail the current standard of care for the treatment of the disease. I will also address the basis for Dr. Trinkaus' complaint to the College regarding Dr. Khan. I will also provide an opinion regarding the treatment provided to the patient on the advice from Dr. Matsumura in addition to providing the usual practice on supervising the care of a cancer patient.

Georgia Karamitsos had synchronous rectal cancer metastatic to liver which was treated with preoperative chemotherapy (FOLFOX) prior to an extended right hepatectomy in July 2012. She then received further chemotherapy followed by chemoradiotherapy to the locally advanced rectal cancer followed by pelvic exenteration. She completed her pseudoadjuvant chemotherapy in April 2013. Despite this curative attempt, she was found to have recurrent disease in the lung, liver and peritoneum in August of 2013. She was advised to start palliative chemotherapy with FOLFIRI + Avastin with Dr. Trinkaus. However, she sought alternative care and started

"SAFE" chemotherapy from November 5 to January 21, 2014 (6 treatments with carboplatin and MESNA). Upon progression, she was treated with DCA, given intravenously.

Although Ms. Karamitsos was diagnosed with stage IV colorectal cancer, the goal of resecting the liver metastasis and the primary tumor are well-accepted treatment goals for such a patient. This is based on long-term data suggesting that up to 30% of patients may be disease-free at 5 years with multimodality therapy[1]. Unfortunately, Ms. Karamitsos developed multiple sites of recurrence with 6 months of completing FOLFOX chemotherapy. As such, the standard treatment would be considered to be FOLFIRI with or without Avastin. This is widely accepted standard not just in Ontario but also across North America and much of Europe. Although the response rate from the GERCOR study reported a response rate of only 4% for second line FOLFIRI, the primary objective of the study was to demonstrate improvement in progression free survival which was observed to be similar in both arms[2]. The Cancercare Ontario guidelines for the use of irinotecan in the second-line treatment of metastatic colorectal cancer clearly supports irinotecan as a single-agent or in combination for patients following the failure of FOLFOX[3]. Furthermore, the NCCN guidelines which are widely accepted in North America, supports the use of FOLFIRI in the setting[4]. In addition the clinical practice ESMO guidelines supports the use of either irinotecan monotherapy or FOLFIRI in those with disease refractory to FOLFOX[5]. It is also widely accepted that exposure to all three cytotoxics (fluoropyrimidines, oxaliplatin and irinotecan) results in the longest survival.

There are only one published phase II data of the use of carboplatin with etoposide but none with MESNA that I could find in the treatment of colorectal cancer in humans[6]. Although Dr. Khan refers to a "FDA approved" phase II trial, it is not referenced in his letters nor could I find the source. In fact, the FDA in the United Status does not approve a clinical trial but rather permits the use of particular investigational agent through an IND exemption. A phase II study is approved by the applicable or local research ethics board and not the FDA. It is important to highlight that the NCCN guidelines, which is rather inclusive for listing treatment options, do not list carboplatin for colorectal cancer. Although Dr. Khan is correct and that cancer patients are often treated with off-label indications, there are either listed in guidelines or often have one or more phase II studies supporting their use (e.g. oxaliplatin in pancreatic cancer) often when no standard treatment exists. However, in receiving carboplatin and MESNA, Ms. Karamitsos did not receive the treatments that are widely accepted as the standard of care.

Ms. Karamitsos was treated for her metastatic colorectal cancer by Dr. Khan under the guidance from Dr. Matsumura. This is unusual and outside the standard of practice of several reasons. There is no documentation that neither Dr. Matsumura, nor Dr. Khan

has received any formal training in oncology. In addition, to my understanding, Dr. Matsumura has never formally met or examined the patient in person. The file provided documents email communication between the two physicians which suggest minimal information being discussed or requested. For example, laboratory tests are listed but the dates of the results are never included. Although I am unaware of any standards for supervising chemotherapy remotely, this practice is in stark contrast to how chemotherapy is ordered and supervised by oncologist but delivered to patients in remote areas by general practitioners in Ontario. In these situations, the patient is always initially seen and examined by the oncologist prior to the initiation of chemotherapy and again seen when a treatment change is required. This includes the review of the staging investigations including review of any radiology. In Ms. Karamitsos' care, the communication does not reflect any such supervision.

The documentation of the Medicor IV treatment also falls below the standard of care. The notes have minimal information in terms of symptoms (e.g. OK, feels well etc.) and the examination is limited to the vitals signs. There is no documentation of any of the symptoms that are often assessed after chemotherapy (e.g. nausea, vomiting, anorexia, diarrhea etc.) nor any documentation of a physical exam. The assessment is limited to "OK" or "stable". The dosing of carboplatin is also unusual in that there is no documentation on the formula used to calculate the GFR.

It would be scientifically valid to examine the efficacy of the low dose carboplatin and MESNA in advanced colorectal cancer in the setting of a clinical trial. This would require a proper protocol, informed consent as well as regulatory oversight from Health Canada and a research ethics board.

Although I do not believe that the cancer treatment Ms. Karamitsos' received under Dr. Khan was harmful, it is the absence of the widely accepted treatment for metastatic colorectal that may have been potentially harmful. In seeking complementary/alternative therapy, the CPSO expects that the physician act in the patient's best interest. In this case, aside from the consent that the patient signed confirming that they are not being offered any medical treatment OR that they have been offered generally accepted medical treatments for her cancer that she has declined, there is no documentation of any extensive discussion with the patient that she has declined conventional therapy. Furthermore, given that the alternative therapy in this case was actually conventional chemotherapy given in an unconventional disease setting, Dr. Khan has not demonstrated any clinical competence (knowledge, skill and judgment) in prescribing and supervising chemotherapy suggesting this is outside the scope of his practice. As stated above, the documentation provided suggests that the clinical assessments performed were below the standard of practice. The CPSO policy also requires that any CAM therapeutic option have a logical connection to the diagnosis and to have a reasonable expectation of remedying or

alleviating the patient's condition. In this case, no published literature supports the use of carboplatin and MESNA in the treatment of colorectal cancer. The only evidence is from the Berkeley Institute in the form of a private communication (as stated by Dr. Khan in his response – "after meeting with him in person and reviewing trial and patient data).

1. Fong Y, Cohen AM, Fortner JG et al. Liver resection for colorectal metastasis. J Clin Oncol 1997 Mar; 15(3): 938-46.
2. Tournigand C, Andre T, Archille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004 Jan 15;22(2):229-37.
3. Members of the Gastrointestinal Cancer Disease Site Group. Use of Irinotecan in the Second-line treatment of metastatic colorectal carcinoma. Evidence-based series 2-16. Archived 2011.
4. Benson AB, Venook AP, Bekaii-Saab T et al. Colon Cancer Version 3.2014. J Natl Compr Canc Netw. 2014; 12:1028-1059.
5. Van Cutsem E, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. Annals of Oncology 21(5)v93-v97.2010.
6. Jeremic B, Acimovic L, Mijatovic L. Carboplatin and etoposide in advanced colorectal carcinoma. A phase II study. Cancer 1993: 1:71(9):2706-8.