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June 2, 2014

Via Facsimile

Ms. Margaret Obermeyer
Investigator
The College of Physicians and Surgeons of Ontario
80 College St.
Toronto ON M5G 2E2

Dear Ms. Obermeyer:

Re: Dr. Akbar Nauman Khan
Your Reference: MMO/93778

Thank you for your letter of May 14, 2014, enclosing the further comments of Dr. Trinkaus.

Please find enclosed Dr. Khan's additional comments on Dr. Trinkaus' most recent letter.

I look forward to hearing from you as to when this matter will be scheduled for consideration by the ICRC.

Yours truly,

McCarthy Tétrault LLP

Lisa M. Constantine

LMC/rk

Encl. Dr. Khan's additional comments on Dr. Trinkaus' most recent letter

25 May 2014

File # MMO/93778

Response to Dr. Trinkaus' Comments

Thank you for providing Dr. Trinkaus' comments to my initial response letter. I only have a few brief comments:

1) I am grateful to see that with the detailed clarification and explanation provided in my initial response dated April 16, 2014, Dr. Trinkaus and I seem to be in agreement with most of the points of discussion. As she has indicated in her letter dated May 13, 2014 "Dr. Khan's points are very well taken and very well received..."
2) I have never disputed that there is "superior evidence" behind the standard approved chemo regimens for colon cancer. In this instance, the response rate of the approved/proven regimen of FOLFIRI chemo offered by Dr. Trinkaus (in a patient who has failed FOLFOX) is 4%. The rate of neutropenia with this approved regimen is 21% and the rate of neuropathy is 24% (J Clin Oncol 2004, reference attached). The patient made an informed choice with full knowledge of what was approved and unapproved. If the approved regimen has phase 3 trial data that confirms it is a minimally effective therapy with significant risks (like in this case), it is sensible for the patient to look for promising alternatives, and not unreasonable to offer them.
3) As stated in my initial response dated April 16, 2014, I do not use any drug that has "proven to be ineffective" in compliance with the CPSO Complementary/Alternative Medicine policy. Dr. Trinkaus has kindly provided many references where carboplatin has been used in colon cancer but none of the references show that it has been "ineffective". I agree with Dr. Trinkaus regarding different level of evidence and also stand behind my statement made in my response dated April 16, 2014 point #3. For the record, the patient Mrs. G.K. is currently undergoing natural therapy with one of her trusted naturopathic doctors, and I am assisting in monitoring the therapy. Through my communication with her family, I can say that they remain satisfied with the decision not to undergo standard palliative chemotherapy, regardless of the outcome of the current therapy.
4) Regarding Dr. Trinkaus' stated concern with Dr. Matsumura's website, the patients who went into long-term remission of up to 7 years with carboplatin + mesna, were not cherry-picked from a large group in order to give a false impression. They were 4 out of 6 consecutive patients.
5) Regarding Dr. Trinkaus' comments about her inability to find "Safe" Chemo trial data, I believe she has understood Dr. Matsumura's letter explaining the withholding of publication for the time being. I also agree with her that communication could have been better. For example, had she requested, I would have had Dr. Matsumura call her to explain the therapy in detail, as I did offer to her in writing. That would have saved her time searching for the trial on the internet, and may have prevented this complaint.
6) I agree that Dr. Trinkaus is entitled to her opinion regarding the best therapy for her patients. The final decision still rests with the patient. It is also the patient's choice to decide who they wish to have involved in or collaborating in their care.
7) The comment about "Safe" Chemo eliminating the marrow toxicity of carboplatin on Dr. Matsumura's website was in reference to his phase 2 trial, and is possible for chemo-naïve patients. We never make

a general claim of zero marrow toxicity or zero side effects of the regimen however, as can be clearly seen in the detailed consent form that we use.

8) I can now understand Dr. Trinkaus' reasons for contacting the CPSO originally and asking for guidance. However, it is difficult for me to understand the CPSO's response. Rather than advising a more collegial initial approach to resolve any issues, the CPSO actively encouraged Dr. Trinkaus to make the complaint. I am not sure why the CPSO did that when their own website advises differently:

> *If you have a concern about communication, records, or if you have questions about the treatment you've received,* ***we strongly encourage you to first speak with your doctor*** *or hospital, if possible, before contacting the College. This is* ***often the most direct way to get the answers that you need. If this is not possible or successful,*** *then we urge you to contact the College for assistance.*
>
> *If your concerns or questions are about the quality or appropriateness of care received, you may need to speak with a College staff member in the Investigations and Resolutions Department who has experience in health care. Staff may be able to answer questions about your care;* ***clarify which questions to take back to your doctor;*** *and/or answer questions about how the health care system works.*

Dr. Trinkaus' letter indicates the College did <u>not</u> ask her to communicate with me or Dr. Matsumura. Instead she was advised to "voice her concerns" to the College.

Looking back and reviewing Dr. Trinkaus' initial letter to the College dated Feb 13, 2014 (received by the College Feb 14, 2014) entitled "Re: concern re: treatment for patient", there is <u>no specific complaint in it</u>. Attached to Dr. Trinkaus' Feb 13 letter was a collection of redacted chart documents for Mrs. G.K. in which there is documentation of a call with me listing some concerns, which I thought were addressed during the conversation. I never received this chart document from Dr. Trinkaus, and did not know the issues she listed were unresolved from her standpoint. Therefore I did not have the opportunity to provide a detailed written response, until such time as the College sent me these documents.

In summary, I believe Dr. Trinkaus and I are now in agreement regarding most of the initial concerns raised. We may disagree on whether patients should always choose therapies solely based on the highest level of evidence (phase 3 trial data). I sincerely hope that is not viewed as a foundation of a complaint or of any sanctions.

Thank you.

Sincerely,

Akbar Khan
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J Clin Oncol. 2004 Jan 15;22(2):229-37. Epub 2003 Dec 2.

FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.

Tournigand C[1], André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A.

Author information

Abstract

PURPOSE:

In metastatic colorectal cancer, phase III studies have demonstrated the superiority of fluorouracil (FU) with leucovorin (LV) in combination with irinotecan or oxaliplatin over FU + LV alone. This phase III study investigated two sequences: folinic acid, FU, and irinotecan (FOLFIRI) followed by folinic acid, FU, and oxaliplatin (FOLFOX6; arm A), and FOLFOX6 followed by FOLFIRI (arm B).

PATIENTS AND METHODS:

Previously untreated patients with assessable disease were randomly assigned to receive a 2-hour infusion of l-LV 200 mg/m(2) or dl-LV 400 mg/m(2) followed by a FU bolus 400 mg/m(2) and 46-hour infusion 2,400 to 3,000 mg/m(2) every 46 hours every 2 weeks, either with irinotecan 180 mg/m(2) or with oxaliplatin 100 mg/m(2) as a 2-hour infusion on day 1. At progression, irinotecan was replaced by oxaliplatin (arm A), or oxaliplatin by irinotecan (arm B).

RESULT:

Median survival was 21.5 months in 109 patients allocated to FOLFIRI then FOLFOX6 versus 20.6 months in 111 patients allocated to FOLFOX6 then FOLFIRI (P =.99). Median second progression-free survival (PFS) was 14.2 months in arm A versus 10.9 in arm B (P =.64). In first-line therapy, FOLFIRI achieved 56% response rate (RR) and 8.5 months median PFS, versus FOLFOX6 which achieved 54% RR and 8.0 months median PFS (P =.26). **Second-line FOLFIRI achieved 4% RR and 2.5 months median PFS**, versus FOLFOX6 which achieved 15% RR and 4.2 months PFS. In first-line therapy, National Cancer Institute Common Toxicity Criteria grade 3/4 mucositis, nausea/vomiting, and grade 2 alopecia were more frequent with FOLFIRI, and grade 3/4 neutropenia and neurosensory toxicity were more frequent with FOLFOX6.

CONCLUSION:

Both sequences achieved a prolonged survival and similar efficacy. The toxicity profiles were different.