Abstract
Serum tumor marker (STM) estimation is often used in clinical practice in monitoring response to treatment and as a predictor of treatment failure and relapse. However, there are pitfalls in interpretation, particularly in the immediate post treatment period, when a rise in titre could be observed, the phenomenon being termed as “flare”. A literature search was done to examine this phenomenon for some of the commonly used serum tumor markers in malignancies. This phenomenon has been documented with respect to AFP, beta HCG, CEA, AC 15.3, PSA, CA 19.9 and CA 125 with or without other evidence of progression. Based on this review, a practical approach is suggested so that the clinician is not misled into changing a potentially effective treatment regime. A practical approach would be to correlate serum tumor marker values with other clinical and radiological parameters, and not to rely exclusively on serum marker values to guide therapy.

Keywords
serum, tumor markers, flares, STM pseudoprogression

Introduction
The routine use of serum tumor markers (STM) to monitor response to chemotherapy is recommended in very few malignancies, but used in many ways in actual clinical practice. In an ideal world, tumors and their markers are required to regress in a linear fashion signaling tumor response; any increase in values would be interpreted as a mark of failure and chemorefractoriness. However, in the less than perfect world of oncology, tumors might actually enlarge in size on imaging, or tumor marker levels increase initially when exposed to chemotherapy drugs, but only to subside later. The latter phenomenon is variously called “flare”, “surge”, “spiking” or ”pseudoprogression” and has misled many medical oncologist into abandoning potentially effective treatment. This article is an attempt to remind the practicing medical oncologist about the phenomenon and to suggest an approach to the problem.

Corresponding Author: Dr. Ajit Venniyoor, MD, DM, Senior Consultant Medical Oncology, National Oncology Centre, The Royal Hospital, PB 1331, PC 111, Muscat, Sultanate of Oman, Email: avenniyoor@gmail.com , Fax: +96824627004, Mobile No: +96897059270

Recommendations on use of tumor markers for monitoring treatment response:
American Society of Clinical Oncology (ASCO) has issued guidelines on the use of tumor markers in the management of various cancers. In summary, as far as monitoring of disease response is concerned, it:

1. Recommends the use of CA 15.3, CA 27.29 and/or CEA only in the absence of readily measurable disease for monitoring response to therapy in metastatic breast cancer (MBC); increasing levels may be used to indicate treatment failure (1);

2. Recommends measuring serum AFP and HCG at the start of each chemotherapy cycle and again when chemotherapy concludes to monitor treatment response or progression during or soon after therapy in germ cell tumors (2);

3. Recommends CEA as the marker of choice for monitoring the response of metastatic colorectal cancer to systemic therapy (3);

4. Does not recommend the routine use of serum CA 19-9 alone for monitoring response to treatment in pancreatic cancer. Serial elevation suggestive of progressive disease must be confirmed with other studies (3).
Mechanism of surge phenomenon

Postulated mechanisms of STM flare include the following:

1. Tumor cell lysis releasing the markers into blood
2. Delayed clearance of the markers due to liver/renal toxicity of chemotherapy
3. Increased production of tumor markers due to direct effect of the drugs on tumor cells.

Serum Tumor Marker (STM) Flares

Serum Alpha feto-protein (AFP):

Germ cell tumors: Tumor markers (AFP and human chorionic gonadotrophin HSG) may show a transient increase in the first weeks post chemotherapy of non-seminomatous germ cell tumors (4). Explanations for the phenomenon include the ongoing production of the glycoprotein by the tumor cells, altered marker metabolism or excretion, and tumor cell lysis with subsequent release of the glycoproteins into the serum. In a large study from Netherlands (5), AFP increased in 29% of the patients studied and HCG in 25% (flare defined as any increase between day 1 and day 8 values). While HCG flare did not have a prognostic significance, flare in AFP was associated with poorer prognosis and a greater surge (more than 30% vs less than 30%) was associated with further worsening. The authors also noted that some patients display second or third surges during subsequent cycles of chemotherapy.

No case of flares involving germ cell tumor of ovary could be found in published literature.

Hepatocellular cancer (HCC): Serial estimation of AFP is used to monitor response to therapy. There have been no reported cases of AFP flares during chemotherapy or targeted therapy of HCC, but AFP flares are known to occur during episodes of acute hepatitis (6) and should be kept in mind.

Human chorionic gonadotrophin (HCG):

HCG flares are known phenomenon associated with treatment of germ cell tumors; however, the Netherlands study (5) did not find any adverse impact on prognosis. Transient gonadal suppression due to chemotherapy may be responsible for increase in HCG levels, but these flares are very small (increasing from below 2 up to 5–8 U/L during chemotherapy).

Flares are not known with treatment of gestational trophoblastic disease (GTD) (which is somewhat contrary to the theory of marker shedding due tumor lysis as a mechanism of the flare). Occasionally, beta-HCG levels can remain marginally elevated post treatment of GTD, a condition called “phantom HCG syndrome” or pseudohypergonadotrophinemia.

Carcino-embryonic antigen (CEA):

Colon Cancer: ASCO guidelines (3) (2006) note that CEA flare can be seen in the first 4-6 weeks after starting chemotherapy. This was based on two small studies (7, 8) that showed that CEA flare (defined as a >20% rise from baseline followed by a >20% drop from baseline in one or more subsequent CEA tests) may occur in 10%–15% of patients with metastatic disease treated especially with oxaliplatin chemotherapy. A larger study from Royal Marsden Hospital (9) (n=670) confirmed this phenomena in 11.6% of patients (with both oxaliplatin and Irinotecan based chemotherapy) and found that the flare was associated with good prognosis.

Postulated mechanisms for flare include 1) tumor cell lysis releasing the protein into the blood stream 2) liver toxicity of chemotherapy releasing the antigen/delaying its clearance from the blood 3) increased CEA production as shown by effect of 5 FU on cell lines (increased CEA messenger RNA transcription and expression)

Breast cancer: CEA is sometimes used, along with CA 15.3 to monitor response to chemotherapy and flares in the initial 4 – 8 weeks have been recorded (1).

Prostate Specific Antigen (PSA):

PSA flare had been associated with initial treatment of androgen dependant prostate cancer with LH-RH agonists (due to increased testosterone levels), and now with the introduction of docetaxel based chemotherapy for metastatic cancer, in the castration resistant cancers as well.
Nelius and Filleur (10) reviewed 4 case series totaling 253 patients. Flare rates ranged between 7.6% and 13.6%. The median duration of a PSA surge/flare-up is 2-3 weeks and can last up to 6-8 weeks. The maximum peak of PSA flare reported in a case was 404% from baseline. There was no prognostic impact. Flare was also reported with second line chemotherapy in about 15% cases(11).

Postulated mechanisms include PSA release from a tumor undergoing lysis, and also transactivation of mutated androgen-receptors by the estramustine component of the therapy, the premedication with dexamethasone and activation of stem cell precursors.

Due to this phenomenon, it is recommended that a minimum of 3-4 cycles of docetaxel be delivered before assessing response. The Prostate Cancer Clinical Trials Working Group recommends that PSA measurements should not be obtained during the first 12 week and that it should not be used as the sole criterion for clinical decision making (12).

**CA 15.3:**

The routine use of CA 15.3 is not recommended for monitoring therapy in any malignancy, except in metastatic breast cancer (MBC) if the lesions are not measurable (such as ascites, pleural effusion or bone metastasis) (1). CA 15.3 flares after chemotherapy has been reported in MBC and has been associated with a significantly higher risk of disease progression. Flares average about 125% above base line (range 30-230%) and can take up to 60-67 days (in one case, up to 101 days) to return to baseline (13).

Surprisingly, the use of granulocyte colony stimulating factors (G-CSF) has been associated with increase in CA 15.3 levels (14).

**CA 19.9:**

Pancreatic cancer: In a small study from Austria (15), 15 of 84 cases (18%) of advanced pancreatic cancer had CA 19.9 flare during the first month of therapy, and this was associated with a trend towards disease progression.

Gastric cancer: In a Korean study (16), both CEA and CA 19.3 flared during chemotherapy of metastatic gastric cancer. The median time to peak and the duration of the CA19-9 surge were 2.3 and 7.1 weeks, respectively. All patients who had flares had radiological evidence of benefit.

**CA 125:**

Epithelial ovarian cancer: CA 125 is thought to be a reliable marker of treatment response in first line treatment with paclitaxel and Cisplatin. Various models have been developed to use CA 125 decline alone as a criteria for response. However, the same is apparently not true in second line. In a study of 120 recurrent ovarian cancers, Gossner et al (17) reported that 59% of Pegylated Liposomal Doxorubicin (PLD)-treated and 18% of topotecan-treated cancers have increasing CA 125 values during the first two cycles before meeting criteria for response at a median of three cycles of treatment. A larger study by Coleman et al (18) (n=409) confirmed this; of the 40 PLD-treated patients who had a response (CR + PR), 17 (43%) had rising CA125 values following the first cycle of therapy. The magnitude of this increase was 25% or greater in one of five responders. Similarly, of the 35 topotecan-treated patients with a response (CR + PR), 4 (11%) have an increase in CA125 after the first cycle. 6% of topotecan-treated patients and 10% of PLD-treated patients were found to have a rise of greater than 25% from baseline even after cycle 2, although ultimately all responded. Thus, the current recommendation to administer two to four cycles of therapy before assessing response seems appropriate.

**Discussion**

STM flares are observed with respect to most commonly used markers. There is no single practical solution to the problem of STM flares. However, some of the possible approaches to avoid before abandoning effective therapies are outlined below.

1. Stick to guidelines. Do not use tumor markers in clinical practice unless this is evidence-based, such as those recommended by ASCO or National Comprehensive Cancer Network (NCCN);
2. Obtain tumor marker levels only after delivering the planned initial dose of chemotherapy (generally 3 or 4 cycles,
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depending on regimen), unless there is obvious clinical and symptomatic progression. Early and repeated sampling can lead to errors and unnecessary anxiety;

3. Don’t depend on tumor marker levels alone to assess response (the sole exception to the rule being HCG in gestational trophoblastic disease) – consider them along with other parameters such as the clinical and imaging picture, and if available, other markers including LDH. PET-CT scan is especially useful in assessing early response, but pseudoprogression has been reported (19);

4. Rule out other (especially benign) causes of marker flare if levels remain elevated despite evidence of regression by other parameters. For example, chronic active hepatitis, liver cirrhosis, sarcoidosis, hypothyroidism, and megaloblastic anemia have all been reported to increase CA 15-3 levels (13). Hepatitis has also been associated with AFP flare, both in HCC and germ cell tumors. Second malignancies (which can also release tumor markers) as a cause for marker flare has not been reported.

Conclusion

Transient increase in serum tumor marker values (flares) on starting chemotherapy has been reported in many malignancies. The exact mechanism is yet to be understood. The practicing medical oncologist needs to be alert with this phenomenon and avoid prematurely stopping potentially effective chemotherapy unless there is definite evidence of disease progression. This can be done by resisting the urge to check early and repeatedly, and by correlating serum tumor marker (STM) values with other parameters, especially imaging.

References


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