Clinics in Oncology

Case Report
Published: 05 Nov, 2019

Case Report of Pathologically Confirmed Complete Response of Metastatic Breast Cancer after Long Term Experimental Antiangiogenic Treatment as Addition to Standard Therapeutic Approach

Mariani G[1], Galli G[1], Marchianò A[2], Regalia E[3], Gianni L[4] and Valagussa P[5]*

[1]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

[2]Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Italy

[3]Fondazione IRCCS Istituto Nazionale Tumori, Italy

[4]Department of Medical Oncology, San Raffaele Hospital Scientific Institute, Italy

[5]Fondazione Michelangelo, Italy

Abstract

Metastatic breast cancer otherwise called stage IV or advanced breast cancer is one among the unspecific types of cancer and is most advanced. It spreads to lymph nodes and to other organs but still considered as breast cancer. Metastatic Breast Cancer (MBC) has remained an incurable disease so Complete Response (CR) in MBC is rare.

However survival rates of patients with Metastatic Breast Cancer has gradually prolonged over the past few years due to improvement of Antineoplastic agents.

Keywords: Metastatic breast cancer; Antiangiogenic treatment; Sorafenib

OPEN ACCESS

Correspondence:
Mariani Gabriella, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, via G Venezian 1, 20133, Milan, Italy, E-mail: gabriella.mariani@istitutotumori.mi.it

Received Date: *20 Sep 2019*
Accepted Date: *25 Oct 2019*
Published Date: *05 Nov 2019*

Citation:
Mariani G, Galli G, Marchianò A, Regalia E, Gianni L, Valagussa P. GTV Cochlea Distance to Predict the Case Report of Pathologically Confirmed Complete Response of Metastatic Breast Cancer after Long Term Experimental Antiangiogenic Treatment as Addition to Standard Therapeutic Approach. Clin Oncol. 2019; 4: 1666.

Introduction

Complete Response (CR) in MBC is rare [1]. Scarcity of data exists in literature about patients' and tumor characteristics, treatment regimens and therapeutic lines associated with this outcome [2-3]. Given the infrequent use of surgery in systemic disease, pathological confirmation of CR is hardly ever obtained [4-7]. Despite advances in the management of breast cancer, metastatic disease is still incurable and new treatment options are needed. Herein we describe the case of a MBC patient obtaining pathological CR after treatment with a combination of cytotoxic, endocrine and antiangiogenic therapy in the setting of a clinical trial.

Sorafenib is a multi-kinase inhibitor with antiangiogenic and antiproliferative activity approved for use in renal and hepatocellular cancer [8-10]. At our institution we have conducted a double-blind randomized trial of Sorafenib *vs.* Placebo in combination with docetaxel and/or letrozole as first-line therapy to investigate the potential benefit of Sorafenib as addition to standard therapeutic approach in patients with HER-2 negative MBC [11]. The study was sponsored by Fondazione Michelangelo and supported by Onyx Pharmaceuticals Inc.

Case Presentation

A 39-year-old hispanic woman was diagnosed in August 2009 with bilateral synchronous Breast Cancer (BC) staged cT1 cN0 cMx at preoperative evaluation. Her past medical history was unremarkable and she did not assume any chronic therapies. Given her strong familiarity for BC, genetic counseling was suggested but refused. On 13 October, 2009 a total bilateral mastectomy with right sentinel node biopsy and left axillary dissection was performed. The pathological examination from right breast and nodal specimens revealed an intermediate grade invasive ductal carcinoma with *in situ* component with positive hormone receptors (estrogen receptor, ER 75%, progesterone receptor, PgR>95%), Human Epidermal Growth Factor 2 (HER2) negative hyperexpression (evaluated by immunoistochemistry) and high proliferative index (MIB-1 30%), staged pT1b (0.6 cm) pN0sn (0/1 axillary lymph node). Pathological report from left side showed a similar histology (intermediate grade invasive ductal carcinoma with in situ component, ER>90%, PgR>90%, HER2

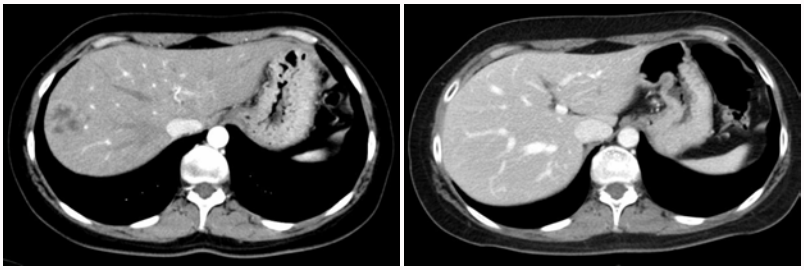

Figure 1: Diagnostic CT scan at baseline (1.1) and at radiologic complete response of liver disease (1.2).

negative, MIB-1 27%) and a more advanced stage pT2 (2.4 cm), pN1a (3/19 axillary lymph nodes). Postoperative staging documented multiple secondary lesions in both hepatic lobes, measuring up to 3.5 cm at the 7th segment.

Liver biopsy was not performed due to patient's refusal and undoubted diagnostic evidence of imaging. Patient was enrolled in a clinical study that was active at that time in our institution, a phase IIb double-blind randomized trial aimed to evaluate the efficacy and safety of sorafenib compared to placebo, when administered in combination with cytotoxic or endocrine therapy in patients with HER-2 negative locally recurrent or MBC (FM-B07-01, INT 07/43 study) [8]. The protocol was approved by the independent ethics committee of our institution; was sponsored by Fondazione Michelangelo and supported by Onyx Pharmaceuticals Inc.

From November 2009 to April 2010 the patient received intravenous docetaxel 75 mg/mq q21 for 6 cycles in association with oral placebo/sorafenib 400 mg twice a day, continuously according to the protocol and the randomization arm. Disease assessments occurred every nine weeks as per protocol. At the end of cytotoxic treatment program, >50% partial response of hepatic lesions was observed. Therefore, prosecution of placebo/sorafenib therapy was confirmed and a maintenance endocrine treatment with letrozole 2.5 mg daily and triptoreline 11.25 mg every 3 months was associated. In June 2010, due to a persistent grade 3 hand-foot syndrome experimental drug dose reduction to 400 mg daily was necessary. Subsequently therapy was continued at this dose.

Computed Tomography (CT) evaluations were systematically performed as per protocol and revealed additional disease response until assumed CR was documented in December 2011. Only a hypodense alteration focused on the 7th segment was persistent but not further definable.

The FM-B07-01- INT 07/43 study closed in January 2013 and unblinding of treatment arms revealed that patient had been given sorafenib. Although no clear benefits of experimental therapy had emerged from the trial, compassionate administration of the drug was permitted after the end of the study in consideration of the clinical benefit. The Fondazione Michelangelo as sponsor of the study dispensed the drug over the time.

In February 2016 the prolonged duration of therapy, the lack of evidence of outcome benefit derived from the study, the absence of data about long term safety of the drug and the reappearance of a low grade cutaneous toxicity suggested discontinuation of sorafenib and continuation of letrozole alone.

A Positron Emission Tomography (PET and PET/CT scans with [18F]-Fluorodeoxyglucose FDG) and a gadolinium-enhanced magnetic resonance of the abdomen confirmed presumptive disease inactivity in the liver, with persistence of hypodense alteration and residual cystic lesions. Given their favorable position, hepatic nodules were considered suitable for radical surgery.

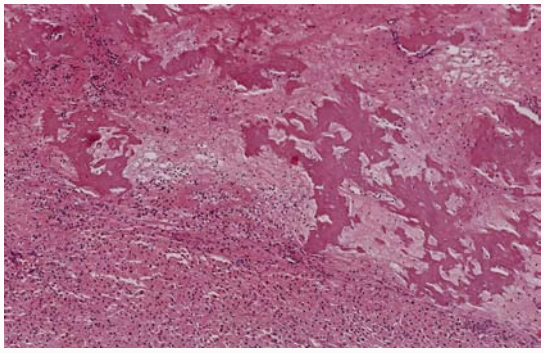

Figure 2: Pathologic findings showing Hyaline fibrosis and Liver parenchima.

Meanwhile, the patient finally accepted to perform genetic testing and BRCA-1 pathogenic mutation was found. Indeed, atypical resection of VI and VII liver segment with consensual bilateral ovariectomy, hysterectomy and peritoneal washing was performed on September 2016. Pathological examination revealed absence of active disease in all surgical specimens; in particular, only fibrotic nodules were observed in the liver. In consideration of iatrogenic menopause, LHRH-analogue was discontinued and patient continued letrozole only. Quarterly follow-up with CT scan was planned. The patient is live and last follow up was done on August 2019 without evidence of disease.

Discussion

MBC has always been considered an incurable disease, as CRs are rare. In fact, scarcity of data exists in literature about patients' characteristics and tumor features associated with this outcome [12]. CR occurs more often in the context of first or second line therapy for metastatic disease, but sporadic cases up to more advanced therapeutic lines have been reported. It is known that CR entails a strong positive prognostic impact at any point of disease history, favorably influencing survival, and even some cases of apparent persistent cure have been described. However, long term outcome of this patients' subpopulation is unknown [13,14].

Given the systemic nature of MBC, surgery has traditionally been excluded from its clinical management and most guidelines do not consider invasive approach beneficial in this setting. However, negative data about surgery have been obtained before the introduction of recent cytotoxic, targeted and hormonal compounds,

which have consistently ameliorated prognosis of MBC [15]. Indeed, a growing amount of data is recently supporting the role of invasive procedures in this setting, similarly to what has become clinical practice in colon cancer. A multidisciplinary approach may be an optimal strategy in particular for oligometastatic disease in young fit patients. Even if the potential of cure for this strategy still remains unclear, a prolongation of disease free survival appears a feasible goal of such an approach [7].

Sorafenib is an oral multitarget tyrosine kinase inhibitor acting on different cellular pathways, in particular Vascular Endothelial and Platelet Derived Growth Factor (VEGF and PDGF respectively) [8-10]. Its efficacy has been demonstrated in hepatic, thyroidal and renal metastatic carcinomas, with a manageable toxicity profile [16-18]. At our institution we have conducted a double-blind randomized trial of sorafenib *vs.* placebo in combination with cytotoxic or endocrine as first-line therapy to investigate the potential benefit of sorafenib as addition to standard therapeutic approach [11]. A total of 218 patients were enrolled, 107 received placebo and 111 sorafenib. Visceral presentation accounted for 75% of the patients and hormone receptor negative tumors were 22%. Best overall response was 43% and 42%, respectively. The median Progression Free Survival (PFS) of placebo was 8.4 month and of sorafenib 8.4 month, HR 1.22 (95% CI: 0.909, 1.616). Overall, 67% of the patients were alive at the time of analysis. Hence, the addition of sorafenib to the best standard treatment did not contribute to a statistically significant improvement in therapeutic efficacy but there was a suggestion of a biologic effect (Figure 1).

The study was part of a clinical development program known as TIES (Trials to Investigate the Effects of Sorafenib in Breast Cancer), where Onyx, in collaboration with investigators and cooperative groups, coordinated four large randomized Phase 2 double-blinded trials with the aim of testing the efficacy of best standard therapy with or without sorafenib in patients with HER2 negative MBC [19]. Unfortunately, from the different studies that have investigated the potential activity of sorafenib in MBC, not evidences of benefit have ever emerged with either single drug or combination therapy so far [20-25]. In particular, at the best of our knowledge, no cases of CR in MBC patients during treatment with sorafenib have been described in literature (Figure 2).

Conclusion

Even if the atypical and experimental therapeutic regimen administered to this patient does not permit to generalize conclusions, we suggest that multidisciplinary approach should always been considered when drawing a long term therapeutic plan in MBC patients. Increasingly new targets were identified but the optimal sequence or combination of agents has not been standardized.

Though CR is a rare event, the possibility of obtaining long term complete remission and sometimes apparent cure of systemic disease should induce clinicians to tailor and personalize therapeutic sequence. Moreover, we suggest that an invasive approach may be beneficial in selected cases.

Clinical Practice Points

Complete Response (CR) in Metastatic Breast Cancer (MBC) is rare. Efficacy of sorafenib in treating MBC has never been proved. Surgery has no established indications in the treatment of MBC. Recent data are supporting the role of surgical procedures in the multidisciplinary management of MBC. We report the unusual case of a MBC patient obtaining CR after long term experimental treatment with sorafenib and subsequent liver surgery.

Acknowledgment

The study was sponsored by Fondazione Michelangelo and supported by Onyx Pharmaceuticals.

References

1. Kontani K, Hashimoto S, Murazawa C, Norimura S, Tanaka H, Ohtani M, et al. Factors responsible for long-term survival in metastatic breast cancer. World J Surg Oncol. 2014;12:344.
2. Decker DA, Ahmann DL, Bisel HF, Edmonson JH, Hahn RG, O'Fallon JR. Complete responders to chemotherapy in metastatic breast cancer. Characterization and analysis. JAMA. 1979;242(19):2075-9.
3. Kobayashi T, Ichiba T, Sakuyama T, Arakawa Y, Nagasaki E, Aiba K, et al. Possible clinical cure of metastatic breast cancer: lessons from our 30-year experience with oligometastatic breast cancer patients and literature review. Breast Cancer. 2012;19(3):218-37.
4. Khan SA. Primary tumor resection in stage IV breast cancer: consistent benefit, or consistent bias? Ann Surg Oncol. 2007;14(12):3285-7.
5. Rashid OM, Nagahashi M, Ramachandran S, Graham L, Yamada A, Spiegel S, et al. Resection of the primary tumor improves survival in metastatic breast cancer by reducing overall tumor burden. Surgery. 2013;153(6):771-8.
6. Thelen A, Benckert C, Jonas S, Lopez-Hänninen E, Sehouli J, Neumann U, et al. Liver resection for metastases from breast cancer. J Surg Oncol. 2008;97(1):25-9.
7. Vlastos G, Smith DL, Singletary SE, Mirza NQ, Tuttle TM, Popat RJ, et al. Long-term survival after an aggressive surgical approach in patients with breast cancer hepatic metastases. Ann Surg Oncol. 2004;11(9):869-74.
8. Weidner N, Folkman J, Pozza F, Bevilacqua P, Allred EN, Moore DH, et al. Tumor angiogenesis: A new significant and independent prognostic indicator in early-stage breast carcinoma. J Natl Cancer Inst. 1992;84:1875-7.
9. Banerjee S, Dowsett M, Ashworth A, Martin LA. Mechanisms of disease: Angiogenesis and the management of breast cancer. Nat Clin Pract Oncol. 2007;4(9):536-50.
10. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, et al. Discovery and development of sorafenib: A multikinase inhibitor for treating cancer. Nat Rev Drug Discov. 2006;5(10):835-44.
11. Mariani G, Burdaeva O, Roman L, Starosławska E, Udovitsa DP, Driol P, et al. A, Double-blind, Randomized Phase lib Study Evaluating the Efficacy and Safety of Sorafenib (SOR) Compared to Placebo (PL) When Administered in Combination with Docetaxel And/or Letrozole in Patients with Metastatic Breast Cancer (MBC): FM-B07-01 Trial. European Journal of Cancer 2011;47(Suppl 2):10.
12. Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol. 1996;14(8):2197-205.
13. Bishop AJ, Ensor J, Moulder SL, Shaitelman SF, Edson MA, Whitman GJ, et al. Prognosis for patients with metastatic breast cancer who achieve a no-evidence-of-disease status after systemic or local therapy. Cancer. 2015;121(24):4324-32.
14. Babtera GV. Metastatic breast cancer: a paradigm shift toward a more aggressive approach. Cancer J. 2009;15(1):78.
15. Chia SK, Speers CH, D'yachkova Y, Kang A, Malfair-Taylor S, Barnett J, et al. The impact of new chemotherapeutic and hormone agents on survival

in a population-based cohort of women with metastatic breast cancer. Cancer. 2007;110(5):973-9.

16. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125-34.

17. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.

18. Moreno-Aspitia A, Morton RF, Hillman DW, Lingle WL, Rowland KM Jr, Wiesenfeld M, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol. 2009;27(1):11-5.

19. Baselga J, Costa F, Gomez H, Hudis CA, Rapoport B, Roche H, et al. A phase 3 tRial comparing capecitabinE in combination with SorafenIb or pLacebo for treatment of locally advanced or metastatIc HER2-Negative breast CancEr (the RESILIENCE study): study protocol for a randomized controlled trial. Trials. 2013;14:228.

20. Bonelli MA, Fumarola C, Alfieri RR, La Monica S, Cavazzoni A, Galetti M, et al. Synergistic activity of letrozole and sorafenib on breast cancer cells. Breast Cancer Res Treat. 2010;124(1):79-88.

21. Isaacs C, Herbolsheimer P, Liu MC, Wilkinson M, Ottaviano Y, Chung GG, et al. Phase I/II study of sorafenib with anastrozole in patients with hormone receptor positive aromatase inhibitor resistant metastatic breast cancer. Breast Can Res Treat. 2011;125(1):137-43.

22. Gradishar WJ, Kaklamani V, Sahoo TP, Lokanatha D, Raina V, Bondarde S, et al. A double-blind, randomised, placebo-controlled, phase 2b study evaluating sorafenib in combination with paclitaxel as a first-line therapy in patients with HER2-negative advanced breast cancer. Eur J Cancer. 2013;49(2):312-22.

23. Luu T, Frankel P, Chung C, Chow W, Mortimer J, Hurria A, et al. Phase I/II trial of vinorelbine and sorafenib in metastatic breast cancer. Clin Breast Cancer. 2014;14(2):94-100.

24. Baselga J, Segalla JG, Roché H, Del Giglio A, Pinczowski H, Ciruelos EM, et al. Sorafenib in Combination with Capecitabine: An Oral Regimen for Patients with HER2-Negative Locally Advanced or Metastatic Breast Cancer. J Clin Oncol. 2012;30(13):1484-91.

25. Yardley DA, Dickson N, Drosick D, Earwood C, Inhorn R, Murphy P, et al. Sorafenib Plus Ixabepilone as First-Line Treatment of Metastatic HER2-Negative Breast Cancer: A Sarah Cannon Research Institute Phase I/II Trial. Clinical Breast Cancer. 2016;16(3):180-7.