Journal of Oncological Sciences 4 (2018) 62–64

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

Acute promyelocytic leukemia after anthracycline containing chemotherapy for breast cancer: Case report and review of the literature

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ARTICLE INFO

Article history:
Received 26 November 2017
Received in revised form
14 January 2018
Accepted 7 February 2018
Available online 23 February 2018

1. Introduction

Breast cancer is the most common cancer in women.[1] New generation anti-neoplastic drugs, especially dose-dense and/or dose-intense anthracycline-alkylayting agent combinations have been shown to be effective and life expectancy has been found to be increased. However longer survival with these drugs is related with the increased risk of therapy related acute myeloid leukemia (tAML).[2–4] AML incidence has been found to be increased in many studies including breast cancer (Table 1). Here we reported a case with Acute Promyelocytic Leukemia (APL) developing after anthracycline containing regimen. Patient received arsenic trioxide (ATO) for APL induction and maintenance and discussed potential benefit of this drug for breast cancer.

2. Case report

62 year old woman admited to the hospital with a mas s in left breast. Invasive ductal carcinoma was diagnosed and modified radical mastectomy was performed on August 2010. Histopathologically tumor was grade II, estrogen and progesteron receptors were 90% and negative, respectively and Her2 was found to be (+++). She diagnosed as Stage IIIA disease and adjuvant chemotherapy containing 4 cycles of cyclophosphamide and doxorubicine followed by 4 cycles of paclitaxel plus trastuzumab were given. After cytotoxic chemotherapy adjuvant radiotherapy was given, aromatase inhibitor was started and trastuzumab was completed to 52 weeks. After 27 months of adjuvant chemotherapy, she complained from fatique and bone pains. PET/CT showed metastatic lesions in right axilla and left iliac bone. Vinorelbin, trastuzumab plus zoledronic acid were prescribed for metastatic disease. Neutropenia developed after one cycle and bone marrow sampling was done with the suspicion of bone marrow metastasis. However bone marrow biopsy showed APL and t(15: 17) was found to be positive. At this time, vinorelbin was stopped due to priority of APL treatment. Anthracycline was not given for APL induction therapy due to prior exposure to anthracycline, co-morbididty (diabetes mellitus). All-trans retinoic acid (ATRA) plus arsenic thyroxide (ATO) were initiated and complete response was obtained then continued with ATRA-ATO maintenance. Fulvestrant plus trastuzumab was given for hormone responsive Her2 positive metastatic breast cancer. After 47 months at the time of breast cancer diagnosis, cerebral metastatis was detected on July 2014. Cerebral metastasectomy was done but she died due to progressive cerebral disease.

3. Discussion

Breast cancer is the most commonly seen malignancy and the leading cause of cancer-related death among females worldwide.[1] Longer survival times have been achieved with new generation anti-neoplastic drugs and the combination of these drugs with trastuzumab in cases with Her2 overexpression. Anti-hormonal drugs and radiation are other effective choices in these cases both in local and systemic control in breast cancer. However the cost of longer survival with much more treatments is the long term different toxicities including MDS and tAML.[5]

Twenty percent of cases with AML and MDS is associated with the use of anti-neoplastic chemotherapy and the prognosis is worse in tAML compared to de-novo cases with AML/MDS. Factors for increased risk of tAML are underlying malignant disease, cytotoxic chemotherapy and irradiation[6]. The most commonly used alkylating agent used in breast cancer is cyclophosphamide and leukemia develops 4–7 years after exposure. The most commonly used topoisomerase inhibitors in breast cancer are doxorubicin and

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Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2018.02.001

Table 1
Therapy-related Acute myeloid Leukemia in cases with breast cancer.

Reference	Subtype	Age	Interval (months)	Cytotoxic chemotherapy	Radiation
[8]	AML-M2	56	53	Cyclophosphamide, Methothrexate, 5fluorouracil, Tamoxifen	+
[9]	AML-M2	42	36	cyclophosphamide Mitoxanthrone, 5fluorouracil, Vincristine,	+
[9]	AML-M2	39	48	cyclophosphamide Mitoxanthrone, 5fluorouracil, vincristine, tamoxifen,	+
[9]	AML-M2	62	108	Cyclophosphamide, Mitoxanthrone, 5fluorouracil, Mitomycin, Methothrexate, Etoposide, Cisplatin,	+
[10]	AML-M2	39	31	Cyclophosphamide, 5- Fluorouracil, Epirubicin,	+
[10]	AML-M2	44	28	Cyclophosphamide Docetaxel, Doxorubicin, Lapatinib, Trastuzumab, Tamoxifen	+
[11]	AML-M2	42	48	Cyclophosphamide Epirubicin, Paclitaxel, 5Fluorouracil, Tamoxifen	+
[12]	AML-M3	51	71	Cyclophosphamide Doxorubicin, Docetaxel, Leuprorelin, Tamoxifen,	+ (Sr)
[13]	AML-M3	36	24	Medroxyprogesterone acetate, Tamoxifen,	+
[14]	AML-M3	43	9	-	-
[15]	AML-M3	69	10	Cyclophosphamide, Doxorubicin, Paclitaxel	-
Presented case	AML-M3	64	20	Cyclophosphamide Doxorubicin, Paclitaxel, Trastuzumab, Anastrazol, Fulvestrant	+
[16]	AML-M5	56	36	Cyclophosphamide, Adriamycin, Oral Anti-estrogen therapy	+
[17]	AML-M5	37	36	Cyclophosphamide, Adriamycin,	+
[18]	AML-M5	59	168	Oral Cyclophosphamide, Methotrexate, 5 fluorouracil, Tamoxifen	+
[19]	AML-M5	54	36	Paclitaxel,	+
[20]	–	50	48	Alkylating Agents, Vincristine, Rtoposide, Teniposide, Paclitaxel, Gemcitabine	–
[21]	AML-M5	56	18	Adrİamycine, Cyclophosphamide	–
[22]	AML-M2	37	18	Cyclophosphamide, Anthracycline, Paclitaxel, Trastuzumab,	+
[23]	AML-M4	78	36	Cyclophosphamide, Methothrexate, 5 fluorouracil,	+
[23]	AML-M2	40	24	Cyclophosphamide, Methothrexate, Tamoksifen	+
[24]	AML-M3	41	12	Cyclophosphamide, 5 fluorouracil	+

AML, Acute Myeloid Leukemia.

epirubicin and leukemia develops within 3 years without pre-leukemic phase and prognosis is better than alkylating agent associated leukemia.[2,7] In our case APL developed 27 months after chemotherapy and this suggests that leukemia was related with doxorubicin using. Table 1 shows 22 cases with leukemia related with breast cancer treated by cytotoxic chemotherapy.[8–24] Six of these 22 cases had APL and 2 cases had been treated by cyclophosphamide, anthracycline and taxanes as in our case.

Overall survival in cases with metastatic breast cancer is variable and it has been found longer survival times in cases treated with anti-Her2 agents.[25–28] Our case died 25 months after development of metastatic disease. Complete metabolic response for breast cancer has been achieved by APL treatment. We did not use anthracycline in our case due to her prior exposure and also co-morbidity. On the other hand ATRA + ATO is the treatment of choice in cases with APL in recent years. It has been reported that complete response rate in cases treated by ATRA + ATO in therapy related APL (tAPL) is between 70 and 90% and median survival time is longer than 3 years. These results suggest that ATRA + ATO is appropriate in tAPL.[26] Response to this therapy was perfect in our case and did not disturb the treatment of metastatic breast cancer. However she died due to cerebral metastasis while she was in complete response for APL and also systemic disease.

Important points for ATO combination in breast cancer is the possible interaction with PI3K/AKT/mTOR pathway and the role of trastuzumab resistance. It has been shown that ATO affects the PI3K/AKT/mTOR pathway and shows an mTOR inhibitor similar effect. Interestingly ATO doses used in clinical practice shows anti-tumor effect in breast cancer cell lines.[27] On the other hand a case with breast cancer and tAPL has been treated by ATO + ATRA and some responses have been reported in metastatic lesions of breast cancer with this treatment. After these results authors designed an in vitro study and showed that RARA gene amplification may be related with response to ATRA.[29] Combining retinoids with trastuzumab maximally inhibits cell growth and induces apoptosis in trastuzumab-sensitive cells.[30] Additionally maximal inhibition of cell growth and apoptosis induction have been shown with the combination of retinoids and trastuzumab in laboratory conditions.[30] These findings suggest that retinoids and/or ATO are effective in tAPL. More importantly these compounds have a potential to increase the response rate in metastatic breast cancer when combined with conventional drugs and reverse trastuzumab resistance which is very important in clinical practice.

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