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Original Research Article

Acute leukemia as second malignancy in primary solid cancer after conventional treatment - A clinico-pathological study

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ABSTRACT

Aims: To study the clinico-pathological features of acute leukemia as second malignancy in primary solid cancer after conventional treatment.
Objectives: To study and compare the demographics, treatment and prognosis of acute leukemia and solid cancer as second malignancy.
Materials and Methods: It's a retrospective study conducted over period of nine years in our centre using computer based data base and medical records as the data source from the department of medical oncology and hematology.
Result: Total 17 patients were diagnosed with primary solid cancers who underwent conventional treatment including surgery, chemotherapy and/or radiation. Majority of cases were female patient (64.7%) with mean age of 58 years (range 39-96yrs) diagnosed as primary solid cancer with stage 3 (52.94%). With stage2 (41.17%). Out of 17 patients, only 4 patients (23.5%) developed acute leukemias which included 3 AML and 1ALL. Of these four patients, only one could be salvaged for about a year with allogenic transplantation while rest three died within a month in an average.
Conclusion: Acute leukemias are one of the worst second malignancies that might occur after conventional treatment in solid cancers which should be regularly monitored during the follow up period.

1. Introduction

The incidence of double primary malignancy is rare[1,2] of which one of the earliest statistical analyses of double primary malignancies was carried out by Bugher in 1934.[3] The insult caused by the chemotherapy and radiotherapy results in morphological changes(dysplasia) as well as cytogenetic alterations(mutations) in hematopoietic cells which initiate the process of second primary malignancy. With recent treatment modalities, cancer patients are surviving much longer with risk to develop metachronous new primary, which might be related to the treatment of earlier. The aim at this study was to report our observation about incidence of acuteleukemia as second malignancy in primary solid cancer treated with conventional treatment. Double primary malignancies could be divided into two categories, depending on the time interval between tumor diagnoses.[4]

Synchronous malignancies are second tumors that occur either simultaneously, or within 6 months after the first malignancy while metachronous malignancies are secondary tumors that develop after 6 months, or even more than that from the first malignancy. The criteria we have used for the diagnosis of double primary malignancies were primarily given by Warren and Gates.[5]

Though the mechanism involved in the development of second primary cancer is still poorly understood, factors Including heredity, constitution, environmental, immunological factors, infective, radiological and cytotoxic treatments have been implicated.[6,7] Chemotherapy and/or

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radiation of patients with primary solid cancers may result in the development of secondary malignancies including acute leukemia with considerable heterogeneity in the incidence of occurrence which could be in part related to the administration of different cytotoxic agents with differences in their dosing. Alkylating agents and radiotherapy are commonly associated with myelodysplasia (MDS) and acute myeloid leukemia (AML) characterized by abnormalities involving chromosomes 5 and 7 with a latency period of 5–7 years.[8] However the latency period after administration of anthracyclines and topoisome rase II-inhibitors is on average 2 years, and cytogenetic alterations include abnormalities in 11q23, translocations t(8;21), t(15;17) as well as inversion 16.[9,10] There is not much evidence of the characteristic features including cytogenetic patterns of patients developing acute lymphoblasttic leukemia (ALL) as a second malignancy in primary solid cancer after conventional treatment.

The current treatment results of patients with treatment-related secondary leukemia remain challenging.

The poor response relates to a larger proportion of patients presenting with old age, high-risk cytogenetics, refractoriness to treatment and increase in co-morbidities that prevents from the administration of intensive cytotoxic induction therapy and haemopoietic stem cell transplantation.[11] Data suggest a 20% to 40% survival at 2–5 years for therapy /treatment related acute leukemia.[12]

2. Methods

This is a retrospective study conducted from Jan 2010 to Jan 2019 in the department of Medical Oncology and Hematology in our hospital HCG Enterprises Limited which is a tertiary care cancer center. The study was initiated using computer based database and medical records as the data source. Acute leukemia as second malignancy was defined as a clinically symptomatic patient with blast cells more than 20% in bone marrow aspiration and biopsy.

2.1. Inclusion criteria

1. Double primary malignancies need to be proved histological.
2. First primary cancer needs to be solid cancer who has undergone conventional treatment (surgery, chemotherapy, +/-radiotherapy)
3. Time interval in between first and second malignancy needs to be minimum 1year duration to avoid synchronous malignancies.

2.2. Exclusion criteria

1. Blood cancer as first primary cancer.
2. Time interval in between first and second malignancy less than 1 year duration.
3. Patient not undergone treatment for either chemotherapy or radiotherapy.

A study pro-forma was created, which included patient identification, primary diagnosis, stage, histological types, treatment received, date of second malignancy, second malignancy diagnosis, conditioning regimen, date of transplant etc. Patient's disease status till the last follow up was recorded along with the prognosis. After the collection of reports statistical analysis was done using SPSS Software. Patients who were lost to follow up after therapy were censored as alive at their last follow up. Descriptive statistics was used for analysis of demographic variables, and disease characteristics.

3. Result

3.1. Patients characteristics (Table 1)

Total 28 patients were diagnosed with dual malignancy during the study period of which 7 patients were having synchronous dual malignancies and hence removed as per our exclusion criteria. Out of 21 patients, 4 patients were having blood cancer as a primary first cancer and hence were removed from our study as per the exclusion criteria. In our study, total 17 patients were diagnosed with primary solid cancers that underwent conventional treatment including surgery, chemotherapy and/or radiation. Majority of cases were female patient (64.7%) with mean age of 58 years (range 39-96yrs) diagnosed as primary solid cancer with stage 3 (52.94%). With stage 2 (41.17%). Breast cancer (41.17%) was the most common cancer followed by gastrointestinal cancers(29.43%).94.12% patients had received chemotherapy while 76.47% patients had received radiotherapy in conventional treatment. Post treatment, 94.12% patients were in clinical remission(CR). Mean conversion time of primary solid cancer to second malignancy was about 78.82months. Out of 17 patients, only 4 patient (23.5%) developed acute leukemia while 13 patients developed second solid malignancies. None of the patients had history of exposure to radiation before the diagnosis of cancer.

3.2. Acute Leukemia characteristics ($)

Out of 17 patients, only 4 patients (23.5%) developed acute leukemias which included 3 AML and 1 ALL. All of the patients were female patients with diagnosis of cancer breast (50%) and cancer cervix (50%). All of them had undergone complete conventional treatment and were in clinical remission post treatment. The mean conversion time of primary solid malignancy to acute leukemia second malignancy was about 60.75 months. Karyotyping and cytogenetic mutation was done in two patients only which was normal in study. Three patients underwent conventional treatment for secondary leukemia while one patient opted

Table 1: Characteristics of the patients with dual malignancy

Characteristics	No. of patients (n=17)	Percentage
Mean Age	58.17	-
Male	06	35.30
Female	11	64.70
Underlying Primary Solid Cancers		
Breast	07	41.17
Cervix/ovary	02	11.76
Prostate	01	5.88
Head and Neck	02	11.76
GIT	05	29.43
Family History	06	35.30
Co-morbidity	10	58.82
Serology	0	-
Habits (Tobacco/Smoking)	03	17.65
Staging		
Stage 1	0	-
Stage 2	07	41.17
Stage 3	09	52.94
Stage 4	01	5.88
Treatment Received		
Surgery	13	76.47
Chemotherapy	16	94.12
Radiotherapy	13	76.47
Post Treatment status		
CR	16	94.12
PR	0	-
SD	0	-
Progressive	01	5.88
Mean conversion time to second malignancy (in months)	78.82	-
Leukemia as second malignancy	4	23.53
Solid cancer as second malignancy	13	76.47

for palliative care. Of these four patients, only one could be salvaged for about a year with allogenic transplantation while rest three died within a month in average.

3.3. Characteristics of acute leukemia versus solid cancer as second malignancy (Table 3)

The fundamental difference in between acute leukemia with solid cancer as second malignancy that we got in our study was acute leukemias was less common to incidence of about 23.5% of total second malignancies in primary solid cancer treated with conventional treatment. Majority of the patients were female with no family history in acute leukemia group while it was even in solid cancer group. The mean conversion time of acute leukemia from primary solid cancer was shorter (about 60.75 months) than the conversion time to solid second malignancy(about 84.38months). In leukemia group only 1 out of 4 patients could complete conventional treatment along with allogenic transplantation while in solid cancer groups 12 out of 13 patients could complete the conventional treatment and could be salvaged.

4. Discussion

The occurrence of multiple primary malignancies, which was thought to be a rare occurrence is being diagnosed more frequently. The diagnosis of multiple primary tumors is now increasing due to an increased awareness of possibility of a second malignancy, the higher use and sensitivity of diagnostic methods as well as the recent improvements in cancer treatment and survival will further lead to higher prevalence of multiple cancers. As patients with history of cancer tend to undergo regular follow-up, this could lead to earlier diagnosis of new malignancies at curable stages.[13] It is well-known that individuals that suffered from malignancy exhibit a 14-20%[14] higher risk of subsequent primary malignancies. Cancer survivors that develop a second malignancy have a higher risk of dying[15] and experience a worsening in their qualities of life.

As per our study during the nine years period, we had total 28 dual malignancies cases of which metachronous dual cancers were more common than the synchronous dual primary cancers. Only 17 patients were selected as per our inclusion and exclusion criteria in our study. Majority of the cases were female patients with breast

Table 2: Characteristics of Acute leukemia Patients (second malignancy)

Characteristics	Case 1	Case 2	Case 3	Case 4
Age	59	49	63	57
Sex	Female	Female	Female	Female
Family History	Nil	Nil	Nil	Nil
Co-morbidity	DM, HTN	DM, HTN	DM, HTN	DM, HTN
Serology	Nil	Nil	Nil	Nil
Habits	Nil	Nil	Nil	Nil
Primary Diagnosis	Cancer Breast(left)	Neuroendocrine cervix	Cancer Breast(Right)	Squamous cell cancer cervix
Staging	stage III	stage III	stage III	stage III
Surgery Received	Lumpectomy	-	Modified radical mastectectomy	Hysterectomy
Chemotherapy Received	5FU, Epiribicin Cyclophosphamide regimen	Carboplatin, Etoposide regimen	5FU, Epiribicin Cyclophosphamide regimen	Ifofsamide, Bleomycin, Carboplatin
Radiation Received	50gy/25#	50gy/25#	66gy/33#	50gy/25#
Post treatment status	Clinical remission	Clinical remission	Clinical remission	Clinical remission
Time duration for second malignancy	95 months	28 months	24 months	96 months
Second Malignancy	Biphenotype ALL	AML non M3	AML M4	AML M4
Karyotype/mutation	-	Normal/ No mutation	-	Normal/ No mutation
Treatment Received	Conventional treatment	Conventional treatment	Palliative care	Conventional Treatment
Regimen of Chemotherapy	BFM 95	Azacytidine followed by 3+7 induction chemotherapy	Tab hydroxyurea	Azacytidine
Allogenic Transplant received	-	Yes	-	-
Status of patient	Expired	Expired	Expired	Expired
Survival duration from primary diagnosis	96.2 months	39.56 months	24.13 months	96.7 months
Survival duration from second malignancy	1.2 months (36 days)	11.56months(347 days)	0.13months(4 days)	0.7 month (21 days)
Attributable factor	? Epirubicin ?Radiation	? Etoposide ?Radiation	?Epirubicin ?Radiation	?Radiation ?Bleomycin

Table 3: Characteristics of acute leukemia versus solid cancer (Second Malignancy)

Characteristics	Acute Leukemia (N)	Solid cancer (N)
Number of patients	4	13
Mean age	57	58.53
Male	0	6
Female	4	7
Family history	0	6
Co-morbidity	4	6
Habits	0	3
Chemotherapy Received	4	12
Radiation Received	4	9
Mean conversion time to second malignancy(in months)	60.75	84.38
Most common malignancy	AML	Breast
Treatment Completed	1	12
Death	4	1
Survivor	0	12

cancer as first primary solid cancer with advanced stages. They had undergone conventional treatment which included chemotherapy and radiotherapy and were in clinical remission for almost five years post treatment. Out of 17 primary solid cancers, only 4 patients developed acute leukemia with mean conversion time of 60.75 months of which the most common were acute myeloid leukemia(AML). Common chemotherapies used in our cases were alkylating agents, anthracyclines and topoisomerase II-inhibitors for about six cycles. All the cases received radiation more than 50gy/25#. However we couldn't find out any karyotype / cytogenetic changes in our cases. Out of 4 cases, only 1 case had undergone allogenic transplant and was salvage for about a year while rest three cases died within a month. Hence in our study acute leukemia as second malignancy was found aggressive clinically with poor prognosis.

The strength of this study lies in the fact that acute leukemia as a second malignancy in primary solid cancer treated with conventional therapy is very rare in incidence along with poor prognosis which we have studied over a period of nine years. However, this is a retrospective analysis which has its inherent limitation of missing data and lack of follow up. Secondly, we have a very less number of patients data and lack of cytogenetic studies, hence we couldn't analyse on etiology as well as cytogenetics of acute leukemia as second malignancy in depth.

5. Conclusion

Acute leukemias are one of the worst second malignancies that might occur after conventional treatment of solid cancers which should be regularly monitored. Haemopoietic stems cell transplantation (HSCT) plays an integral role in the treatment of patients with acute leukemia as second malignancy. Treatment of acute leukemia as second malignancy is particularly challenging on our setting as it requires a well developed tertiary cancer care centre with Heamopoietic stem cell transplantation unit(HSCT).

6. Source of Funding

Nil.

7. Conflict of Interest

The Author(s) declare(s) that there is no conflict of interest.

8. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

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