CML as Part of Dual Malignancies—A Retrospective Analysis: Possible Mechanisms and Review of Literature

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Abstract Introduction of imatinib has changed the outlook of chronic myeloid leukaemia (CML) patients with overall survival approaching general population. Long term survival in CML patients has provided an opportunity to better study natural history and long term complications of disease as well as the treatment modalities. To study the occurrence and association of other malignancies with their outcomes in patients with CML. This is a single centre retrospective study. All CML patients case records registered with haematology clinic of a tertiary care centre in North India from 2001 to 2014 were perused and evaluated for dual malignancies. Those patients with dual malignancies were personally examined and interviewed if alive. Out of 1677 patients, 15 cases had co-existent malignancies. Four of fifteen cases of dual malignancies had CML as secondary cancer. Three had synchronous and rest 12 patients had metachronous malignancies. Only one patient was in accelerated phase, rest all were in chronic phase. Median age of the dual malignancy cases was 50 years (25–66 years), much younger than reported in west. The initial dose of imatinib was 400 mg OD in all except one.

We did not find any causal association between CML or imatinib therapy with development of secondary tumours. Interestingly in this series, incidence of CML as secondary or synchronous malignancy was higher than earlier published studies.

Keywords CML · Synchronous malignancy · Secondary malignancy

Introduction

The occurrence of second malignancy in a patient with a known malignant tumour is not very uncommon [1]. Based on the time gap between the detection of two malignancies, these are labelled as synchronous or metachronous [2]. Metachronous malignancies are a common occurrence amongst solid malignancies, with incidence much lower in haematological malignancies. Though many authors have described occurrence of secondary malignancies in chronic myeloid leukaemia (CML), there are very few publications on CML presenting as secondary malignancy [3].

CML is the commonest myeloproliferative neoplasm characterised by prolonged asymptomatic period with gradual development of splenomegaly, culminating in acute leukaemia amongst untreated patients. The natural history of disease has been significantly modified post introduction of tyrosine kinase inhibitors (TKI's) therapy with many patients having near normal survival [4]. The present guidelines still suggest lifelong therapy for CML with few ongoing discontinuation trials [5–9]. Concurrently, TKI's have lately been implicated in other immunomodulatory and immunosuppressive effects by acting through T cells [10–12]. Based on the above three factors of near-normal survival, lifelong TKI therapy and TKI

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mediated T cell modulatory action, there has been growing concerns of secondary malignancies in TKI treated CML [13].

Patients and Methods

This is a single centre retrospective study including all CML patients registered with the haematology clinic of a tertiary care centre from North India. Personal details, presenting symptoms, clinical findings, histopathological investigations and disease details of CML/co-existent malignancy were obtained either by direct interviews among patients who were alive or by hospital record reviews (in patients who succumbed to their illnesses). Inclusion criteria include satisfying all the following: age >12 years, diagnosis of CML, patients enrolled after 2001 and diagnosis of second malignancy. Patients with incomplete records were excluded from the study. CML was defined based on the NCCN 2014 guidelines and remission status was defined based on ELN guidelines [9]. Second malignancy was defined as histopathology proven malignancy in the same individual occurring either prior or later to the detection of CML [2]. Synchronous malignancy was defined as second malignancy within 2–6 months of diagnosis of the 1st primary tumour and metachronous malignancy was defined as more than 6 months after diagnosis of 1st primary malignancy [2].

Results

During a 15 year period (January 2001 to December 2014), a total of 2183 patients of CML were registered with the adult haematology clinic of PGIMER, Chandigarh of which 1677 patients were included where complete patient details were available. A total of 15 patients were found to have co-existent second malignancy with CML (Table 1 and Supplement 1). Four patients had CML as the secondary malignancy. Among 15 patients, three patients had synchronous and 12 had metachronous malignancy. The median age of the patients was 50 years (25–66) at the time of diagnosis in this series. Of the 15 patients five were male and rest 10 were female. None of our patients were on 2nd line TKI (Nilotinib and Dasatinib). Two of these 15 patients were in accelerated phase and none in blast phase at the time of diagnosis. History of smoking was present in only one patient who developed bladder cancer and one patient consumed alcohol in non cirrhogenic doses. None of our patients had history of any carcinogenic exposure. Median duration of imatinib therapy in patients with secondary malignancy was 45.5 months (5–130 months). Median duration of follow up was in patients with dual

malignancies. Two patients with dual malignancies succumbed to their illness because of blast crisis and one among them was lost to follow up for last 1.5 year. None of the patients of CML succumbed to the co-existing malignancy.

In patients with CML presenting as primary malignancy (patient no 1–8) the median interval until development of secondary malignancy was 62.3 months (ranged from 8 to 240 months). Whereas, in patients with CML presenting as secondary malignancy the median interval of development of CML was 118.5 months (range 60–144 months).

None of our patients of co-existent malignancy with CML underwent bone marrow transplantation. Cumulative incidence of second cancer (all categories) in our CML patient cohort is 0.0089. Accordingly, within the limitations of the number of patients which are enrolled in this retrospective analysis, the total number of cases of cancer could be in accordance with the incidence of cancer in the Indian population.

Discussion

CML is amongst the most easily treatable malignancies post introduction of imatinib [14]. The current and future research is now focussed on curing this disorder [5, 6]. Diagnosis of SM is important both owing to its impact on overall survival and the morbidity of the individual. This becomes especially important with life expectancy of CML patients nowadays approaching general population. In a study by Roy et al. [15], six out of total 189 CML patients had SM. They also showed increased incidence of prostate cancer amongst SM in these TKI treated patients when compared to general population. However soon in 2006, Pilot et al. published their work on SM and demonstrated the equal incidence of propensity of malignancies in TKI group and general population. This study was sponsored by Novartis Oncology group [16]. We discuss the topic under four major headings: (a) Secondary malignancies in CML during the pre-imatinib era, thus trying to discern if earlier treatment modalities or CML per se predisposes to the secondary malignancy. (b) Secondary malignancies in CML post-imatinib introduction, emphasising on the possible ways by which TKI can cause secondary malignancy. (c) CML presenting as secondary malignancy, this is rarely reported. (d) Limitation of the current study.

CML Presenting as Secondary Malignancy

There is scarcity of published literature on CML presenting as secondary metachronous. We could find an isolated case report by Ural et al. [3], of a 51 year old woman, who

Table 1 Disease characteristics of other malignancy in patients with CML/dual malignancy

Pt no.	SM diagnosis (m/y)	Age at diagnosis of SM	Site	Treatment	Family history	Smoker	Interval between CML/Other malignancy (m)	Date of Imatinib	Interval between Imatinib and SM (m)	Status of SM
1	6/2013	61	Right buccal mucosa squamous cell carcinoma	Wide excision with functional neck dissection	No	No	240	8/2002	130	CR
2	12/2004	25	Breast (bilateral) fibroadenoma	Observation	No	No	8	7/2004	5	Non progressive
3	5/2013	64	Cervix squamous cell carcinoma	LFU	No	No	74	7/2007	72	LFU
4	8/2010	64	Eyelid left pilomatrixoma	Excision	H/o breast carcinoma in mother	No	49	8/2008	42	CR
5	5/2014	72	Colon adenocarcinoma	Resection/ anastomosis + chemotherapy	No	Alcohol consumption non cirrhotic doses	77	5/2009	72	CR
6	7/2012	51	Bladder Ca stage I transitional cell carcinoma	Transurethral resection of bladder tumour	No	Yes	18	6/2011	13	CR
7	3/2012	46	CLL	Chlorambucil + wysolone × 36 cycles	No	No	11	6/2011	9	PR
8	11/2013	27	Pituitary adenoma	Excision + hormonal replacement therapy	No	No	24	7/2011	21	CR
9	10/2007	62	Papillary thyroid carcinoma	Hemi thyroidectomy + thyroxine suppl.	No	No	1	11/2007	0	CR
10	4/2014	32	Breast (right) fibroadenoma	Observation	No	No	0	4/2014	0	Non progressive
11	8/2014	66	PTCL IPI-3/5	Chemotherapy (CVP)	No	No	0	9/2014	0	Completed 5 cycles → CR
12	10/1996	32	Papillary thyroid carcinoma	Hemi thyroidectomy + thyroxine supplementation	H/o insulinoma in father	No	144	11/2008	NA	CR
13	5/1997	22	Juvenile nasal angiofibroma	Excision by lateral rhinotomy	No	No	132	4/2011	NA	CR
14	1/2002	46	Breast adenocarcinoma	Mastectomy + axillary node dissection + adjuvant chemotherapy	No	No	138	7/2014	NA	CR
15	12/09	48	Ca breast adenocarcinoma (right)	Right breast lumpectomy + axillary node dissection + RT + letrozole chemotherapy	No	No	60	11/2014	NA	CR

LFU lost to follow up, PR partial remission, CR complete remission, IPI international prognostic index, NA not applicable, CVP cyclophosphamide + vincristine + prednisolone, RT radiotherapy

developed secondary CML after 4 years of receiving radiotherapy for Ca Cervix. Shimizu et al. [17] studied nuclear atomic survivors of Hiroshima/Nagasaki and proposed a causal relationship of radiation exposure and development of CML after a latency period of 2–25 years. There is no other convincing data regarding the association of CML and radiation exposure.

In our series we have four patients of CML presenting as secondary metachronous malignancy. Only one among these four patients had received radiotherapy in our series. Our patients were predominantly treated with surgery and adjuvant chemotherapy. Two of four patients had breast carcinoma. We also had a rare association of juvenile nasal angiofibroma with secondary CML.

Synchronous Malignancy with CML

CML presenting as synchronous malignancy is reported only thrice in literature (Supplement Table 2). The median duration of primary to secondary malignancy is more than 6 months in all except two patients wherein the two malignancies were detected simultaneously (Fibroadenoma breast—Patient 10; PTCL—Patient 11—Supplement Figure 1) and the third patient of papillary thyroid carcinoma (Patient 9—Supplement Figure 2) where the time gap was 1 month.

Secondary Malignancies in CML: Pre-imatinib Era

Prior to TKI's, interferon was the frontline agent for treating CML (Supplement Table 3). Multiple retrospective studies suggested occurrence of secondary malignancy in CML patients post interferon therapy [13, 18]. Reburu et al. [13] reported 125 cases of secondary malignancies in a population based study including 2735 patients of CML. A predilection to prostate malignancy was reported by multiple authors. Whereas, of the six secondary malignancies amongst 392 CML patients reported by Bhatia et al. [19], none affected prostate (all had either cervical or oral cancers). Study from animal models have shown increased frequency of malignancies of parathyroid, stomach, adrenal, renal and urinary system in rats who received imatinib of 60 mg/kg/day [20]. The same findings with one to one association have not been established in human studies till now, however with reporting of more and more secondary malignancies the concern regarding the oncogenic potential has certainly increased.

Secondary Malignancies in TKI Treated CML

It's been over a decade since imatinib was approved for CML. Lately with increased reporting of secondary malignancies (Supplement Table 4); concerns have been raised over carcinogenic potential of imatinib.

Retrospective study on CML population have been done by different groups worldwide namely Czech Republic group, German CML group, Japanese group, Swedish Cancer study group and all have found increased incidence of secondary malignancy (SM) in imatinib treated patients as compared to general population [13, 21, 22]. Multiple postulates have been suggested to explain the development of secondary malignancies following imatinib therapy (Supplement Table 5).

The median interval of imatinib therapy before onset of secondary malignancies has been reported variably, in our series among 8 patients with CML presenting as primary malignancy, the median duration of TKI therapy was 45.5 months (5–130 months) before development of secondary malignancy. Authors have reported secondary malignancies with predilection to specific organs/body sites, particularly head/neck, cervical and prostate [15, 19, 23]. This site predilection would be influenced by various other factors including regional prevalence, eating habits, smoking behaviour, physician reporting etc. We in our series had not observed any specific site predilection. We had some rare associations such as pilomatrixoma (Patient 4—Supplement Figure 3) and pituitary adenoma (Patient 8—Supplement Figure 4) which were never reported in the literature with CML.

Improved survival of CML in post-imatinib era, have simultaneously led to increased exposure to TKI. The carcinogenic potential of imatinib is still a point of debate with no clear evidence for the same. More dedicated studies are warranted to prove causal association between imatinib exposure and development of secondary malignancy.

Relevance in Asian Scenario

The importance of reporting of SM in TKI treated patients is especially important among Asian patients for two reasons: Primarily, as compared to Caucasians, the age at diagnosis of CML is approximately one decade earlier, (median age being amongst Asian patients at the time of diagnosis of CML is 40 years thereby placing them at higher lifetime risk of acquiring SM [24]. Secondly, Asians have higher trough levels of imatinib for the similar dose as compared to Caucasian counterparts [25, 26]. Thus more studies are warranted involving large cohorts to answer these concerns.

Limitations

The major limitation was the retrospective nature of the study. The actual incidence would have been higher considering some patients with second malignancy not reporting to haematology clinic were lost to follow or died

of the same. We cannot comment about the background incidence of cancer among the referral general population for comparison. We have neither conducted any genetic studies nor family screening for studying genetic basis for these co-existent malignancies. We neither studied the trough levels of Imatinib, nor the association of Imatinib with secondary malignancies in these patients.

Conclusion

We found very low incidence of secondary malignancies in patients of CML. Notably we have higher number of patients with CML presenting as secondary malignancy. We have two cases of synchronous malignancy with CML. Our case series indicates that imatinib isn't a major culprit in our scenario. Further genetic and family studies are warranted prior to commenting any associations in this patient subset.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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