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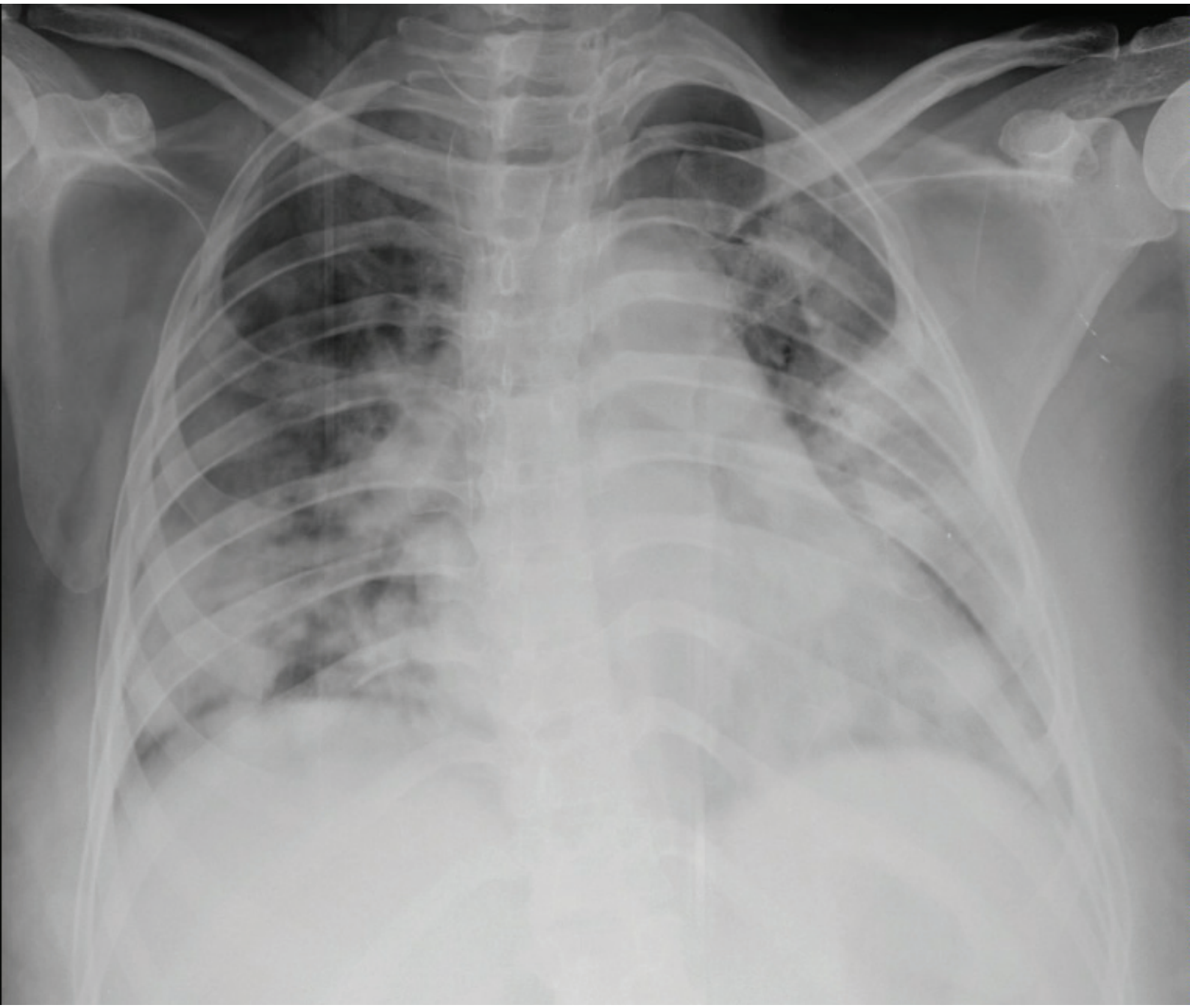

Official Journal of The Sri Lanka College of Oncologists

Cover Page: A Chest X-Ray of a 42 year old patient with breast cancer treated for COVID-19 pneumonia.

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Editorial
COVID-19 and cancer care: Impact, lessons learned and way forward.

Gunasekera S.

It is safe to say COVID-19 has had a profound and long lasting impact on cancer care, not only in Sri Lanka but the entire world. Its no secret that health systems were ill prepared to deal with the tsunami that was COVID-19 and this had drastic spillover effect on cancer care which was already stretched to the limit in terms of manpower and physical resources[1]. One year in to the pandemic, most health systems have recovered from the initial disorganized scramble to provide effective cancer care amidst all the challenges. However, cancer care still hasn't recovered to at atleast the pre-pandemic levels in many of the Low Middle income Countries (LMICs)[2].

The problems the health system faced in Sri Lanka due to COVID-19 pandemic, evolved with time. Initially the main issue was difficulty in patients accessing health care facilities due to travel restrictions imposed by government to curb the spread of the virus. In a country like Sri Lanka where cancer care delivery is mostly centralized this was a significant problem[3]. With easing of travel restrictions medicinal shortages came to the forefront s a major problem. Sri Lanka imports almost all the medical products and supply chain disruption due to the pandemic was the major cause for these shortages. In Sri Lanka we have faced three prominent waves of infections. Anecdotal evidence suggest that proportionate to the infection rates in the general public, infections in patients with cancer had also risen. This in turn resulted in disruption in cancer care as clinical reasons warranted delays, reduction in intensity or complete omission of some modalities of treatment. Effective cancer care involves many personnel representing multitude of different disciplines. Continuous communication, training and obtaining feedback from everyone involved is crucial in successful delivery of cancer care. In Sri Lanka during the pre-pandemic era, most of these interactions occurred as in person meetings, seminars and workshops. All of this came to an abrupt halt with the onset of the pandemic. Although, not quite obvious at the start, this problem can have a lasting negative impact on cancer care in the coming days as well.

Sri Lanka cancer care system took several steps to mitigate the harmful impact of covid on patients with cancer. The response also evolved in parallel with the prevalence of the disease, emerging evidence on COVID-19 pandemic and cancer care, availability of the COVID-19 vaccine etc. Strengthening the infection prevention processes formed the cornerstone of all interventions. Telemedicine solutions which were virtually non existent in the Sri Lankan cancer care space was also employed by many centres with varying degree of success. Clinical practices were also modified to suit these novel challenges. Switching to hypo-fractionated radiotherapy regimes, more out patient based chemotherapy delivery, maximizing the resources available in oncology units in peripheral hospitals, reducing "routine" clinic visits are some of these modifications.

With wider availability of COVID vaccinations and better understanding of the COVID-19 disease process in patients with cancer now Sri Lankan cancer care delivery system is gradually returning to the pre-pandemic baseline. However, it is becoming quite evident that some of these innovations have a role to play in the post-pandemic era as well. Infection controle measures have resulted in reduction of non COVID-19 infections as well, hypo fractionated radiotherapy and outpatient chemotherapy regimens which have been proven to be non-inferior to conventional protocols might be the answer to long radiotherapy waiting lists and congestion in oncology units experienced in Sri Lanka today[4]. Bypassing peripheral oncology units and patients converging to more "Well-Known" hospitals has been a problem in Sri Lanka and during this pandemic has been an eye opener for many patients regarding quality of care that can be delivered by oncology units closer to their residences[5].

COVID-19 pandemic has thrown up many a challenge to the Sri Lankan health system in general and oncology care delivery in particular. However, these challenges have given the

impetus for Sri Lanka to rethink its cancer care models, adapt where necessary and embrace technological innovations. If these positive changes are incorporated into the "New-Normal", we might look at the COVID-19 pandemic as a blessing in disguise in the not too distant future.

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Does the delay in offering adjuvant radioactive iodine for differentiated thyroid cancers matter?

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Abstract

Background: Adjuvant radioactive iodine (RAI) therapy following surgery for differentiated thyroid cancers is the standard of care. The optimal timing to initiate RAI therapy remains unclear. There is a significant delay in offering the adjuvant RAI due to limited resources and the rising demand. The purpose of this study is to assess the delay in offering RAI and the impact of such delay on recurrence.

Materials and Methods: This is an institutional based descriptive retrospective study conducted at the Tellipalai Trail cancer hospital. Patients referred between 1st of April 2012 to 31st October 2019 were included in the study. Data was collected from patients' records and using SPSS (Statistical Package for Social Science 23rd version).

Results: A total of 150 patients were included in the study. Majority of the patients were females (86%). The mean age was 43.6. Eighty five (n=128) percent of patients had papillary carcinoma. Patients with low, intermediate and high-risk disease were 87%, 11% and 2.0% respectively.

Eighty two percent of patients did not received RAI within the recommended 12 weeks. Only three (2%) patients have experienced recurrence. Among those recurred, two patients experienced local recurrence and one regional recurrence. None of the patients died of thyroid cancer.

Conclusion: The recurrence rate was very low in spite of the delay in getting RAI treatment. Extended studies are needed to assess the impact of delay on outcomes.

Keywords: *DTC, RAI therapy, delay in treatment, recurrence*

Introduction

The incidence of differentiated thyroid cancers (DTC) is on the rise globally and locally. The steady rise in the incidence of DTC in Sri Lanka has been well documented (1). The published Sri Lankan National cancer statistics reveals thyroid cancer to be the 2nd commonest malignancy among females accounting for 11% of all female malignancies (2). Overall, it's the 5th commonest malignancy accounting for 7% of all cancers in Sri Lanka (2).

The management of DTC include total thyroidectomy followed by suppression of thyroid stimulating hormone using thyroxin and adjuvant radioactive iodine (RAI) therapy based on the risk assessment. The RAI ablates the remnant thyroid tissue and the microscopic disease leading to lower local recurrences and mortality(3). The ablative dose of RAI depends on the risk category (3).

The optimal time to initiate RAI therapy after surgery remains unclear(4). The published guidelines recommend commencing RAI treatment within 12 weeks of surgery(4).

Though, the Sri Lankan government has invested on improving the availability of RAI therapy, the supply is inadequate to cope with the rising demands leading to longer waiting times than the recommended duration.

Hence, this study was carried out to find out the implications of offering RAI therapy well after the recommended duration.

Materials and Methods

This was a descriptive retrospective study that included all patients above 18 years of age and was diagnosed with DTC and have undergone total thyroidectomy and adjuvant RAI therapy. Patients referred to the Teaching Hospital of Jaffna or the Tellipalai Trail Cancer Hospital

between 1st of April 2012 to 31st October 2019 were included in the study. Patients diagnosed before April 2012 were excluded as there were no hospital-based records.

The relevant data was retrieved from the patient records. Median duration of follow up was 21 months. Ethical clearance was obtained from the Ethics Review Committee, Faculty of Medicine, University of Jaffna.

Data analysis

Data analysis was done using SPSS statistical software. Patients were classified into low, intermediate and high risk according to the 2015 American Thyroid Association Guidelines (5)

Simple descriptive statistics was used to present baseline characteristics of participants eligible for the study. A closeout date for the study was defined as earliest of the last dates of follow up of the patients who were alive and not lost to follow up. Follow-up time for each participant was defined as a time from study entry to the date of last follow up or the closeout date.

Results

A total of 150 patients were included in the study. The baseline characteristics are shown in table 1. The mean age of the participants was 43.6 years and majority were females (86%). Eighty five percent of patients had papillary carcinoma and only 30% of the patients had lymph node metastasis. Table 2 illustrated the risk categorization of the cohort. Majority of the patients (87%) had low risk disease.

Table 03 shows the time interval between surgery and RAI therapy. Only 18% of patients received RAI within the recommended 12 weeks. One third of the cohort received the recommended treatment after 6 months.

Characteristic	Variable	No. of patients (%)
All patients		150 (100%)
Gender	Male	21 (14)
	Females	129 (86)
Age	Mean (Range)	43.6 (19 – 73)
Histology	Papillary	128 (85)
	Follicular	22 (15)
Focality	Unifocal	90 (60)
	Multifocal	60 (40)
LVSI*	Yes	32 (21)
	No	118 (79)
Resection margin	Not involved	147 (98)
	Involved	03 (02)
Lymph node metastasis	Yes	30 (20)
	No	120 (80)

Table 01: *Baseline characteristics; *Lymphovascular space invasion*

Low	131 (87)
Intermediate	16 (11)
High	03 (02)

Table 02: *Risk categorization according to American Thyroid Association guidelines 2015*

Only three patients experienced recurrences and the details given in table 04. All three patients had low risk disease that was resected with clear margins. Two of them recurred in the local site and one in the regional nodes. None of these patients received RAI within 12 weeks. The patient who recurred in the regional nodes received RAI in 16 weeks. The patients who recurred locally had RAI at 37 and 116 weeks. None of the patients failed in distant sites. All patients were alive at the last follow up.

Duration between surgery & RAI	No. of patients (%)
<13 weeks	27 (18)
13 -26 weeks	77 (51)
>26weeks	46 (31)

Table 03*: Time interval between surgery and RAI*

Variable	Patient 01	Patient 02	Patient 03
Type of recurrence	Regional	Local	Local
Time between surgery and RAI (weeks)	16	116	37

Variable	Patient 01	Patient 02	Patient 03
Risk category	Low risk	Low risk	Low risk
Age	35	43	41
Histology	Papillary	Papillary	Follicular
LVSI#	No	No	No
Lymph node metastasis	No	Yes	No
Resection margin	free	free	free

Table 04: *Details of patients with recurrence; # Lympho-vascular space invasion*

Discussion

Radioiodine therapy had been used in the treatment of DTC for many decades with proven benefits (6). It reduces recurrence rate by 33% ($p< 0.001$), compared to thyroid hormone therapy alone (7).

Though the recommendation is to offer RAI within 12 weeks of surgery, there are many challenges in meeting this requirement. Some of the important limitations include huge cost per patient and need for specialized facilities with appropriate radiation protection requirements to administer the treatment. The rising incidence of thyroid cancers have a significant financial implication on the health system, especially in a resource limited country like Sri Lanka.

Non-inferiority of the low doses (1.1GBq) of RAI compared to higher dose (3.7GBq) has been well proven in the HiLo trial (8) and further confirmed in a meta-analysis (9)

This has reduced the cost of RAI therapy per patient and given the opportunity to offer treatment as an out-patient procedure. The Sri Lankan Health Authority has expanded the facilities offering RAI therapy across the island. However, the expanded services are not adequate to meet the increasing demand.

Though DTC is potentially curable, the cancer diagnosis creates significant anxiety to the patients. This is further aggravated by the delay in offering the recommended treatment. Hence, this study was performed to understand the impact of delay on outcomes.

In the present study, 82% of patients did not receive RAI within the recommended period of 12 weeks from surgery. Among the 150 patients, only three patients experienced recurrence despite the delay. All 3 patients had low risk disease which had been excised with clear margins. None of them had aggressive histological variants. The patient who recurred in regional nodes had received RAI after 16 weeks and the two patients who recurred locally had significant delay of 37, 116 weeks. Eighty percent of patients who had RAI beyond the recommended duration never recurred.

This issue had been addressed in some studies with conflicting results. A Japanese study has reported the risk of death to be 4.22 times higher in patients treated by initial RAI after 180 days (26 weeks) after total thyroidectomy compared to those treated within 180 days (10). A recent study from China, reported a delay of more than 12 weeks in offering RAI led to incomplete response in low-to intermediate-risk DTC. They recommended timely RAI therapy for non–high-risk DTC patients. Rafael et al. compared outcomes in patients treated within 6 months vs after 6 months and reported that timing does not interfere with initial response. (11) The present study did not reveal significant adverse outcomes due to delay. This may be because, majority of the patients (87%) having low risk disease. Further, the benefit of RAI in low risk disease had been question in many studies (12). The prognosis of DTC is excellent with reported 10-year survival of more than 95% (13). Hence, a larger cohort with longer follow up may be needed to understand the biology and the behaviour of DTC in Sri Lanka. Such studies will not only contribute towards the health economics and patient satisfaction, but will also enable us to develop our own treatment guidelines for DTC.

Limitations

We acknowledge the limitations of this study. Firstly, it was a retrospective study. Secondly, the study was not powered to detect significant number of events.

Conclusion

According to the present study delay of more than 12 weeks in administering radioactive iodine had minimal impact on outcomes. However, further extended study with a larger number of patients is needed to confirm this finding.

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Complete Remission Rates and Survival of Adult Acute Lymphoblastic Leukaemia Patients Following Remission Induction in a Tertiary Care Cancer Referral Centre in Sri Lanka

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Abstract

Introduction: Adult Acute Lymphoblastic Leukaemia (ALL) patients in Sri Lanka are managed with chemotherapy only regimens and response to treatment is assessed only morphologically. The induction phase of chemotherapy is the key to managing ALL. There is no data in this resource-limited setting on complete remission (CR) rates or survival.

Objectives: To describe the CR rates on day 8 and at the end of induction, to establish the overall survival (OS), disease-free survival (DFS), induction mortality (IM) and common complications during the induction phase of treatment.

Methods: A prospective, observational, analytical, cohort study was carried out to include all newly diagnosed, adult, denovo ALL patients above 15 years of age, admitted to National Cancer Institute, Maharagama from 01st of April 2016 to 31st of March 2017 and were followed up for 2 years after the last patient had completed induction treatment.

Results: Seventy-three adults were diagnosed with ALL. The median age was 29 years. Twenty-nine (39.72%) were between 15-24 years. Male to female ratio was 1.8:1. Forty (54.8%) were of B-ALL phenotype of whom Philadelphia (Ph) chromosome was tested only on 11. CR on day 8 was 74.24% and on day 29 was 92.15%. Induction mortality (IM) was 44.62% with deaths during induction accounting for 51.22% of total mortality for 2 years of follow up. Neutropenic fever and sepsis were by far the commonest complication resulting in 62.07% deaths during induction. Two-year OS was 35.9% with a DFS of 34.38%.

Conclusions: Adolescents and young adults comprise a major proportion of adult ALL and a considerably large proportion of T cell phenotype was found. A trend towards poor prognosis among B-ALL patients was observed which could be due to Ph+ ALLs not being detected and appropriately treated. Although CR rates at the end of induction reached high levels, OS was considerably low with a significantly high IM.

Key words: Acute lymphoblastic leukaemia, Prognostic factors, Induction mortality, Survival, Complete remission rate, Sri Lanka

Introduction

According to the National Cancer Control Programme in Sri Lanka, more than 2000 cases were reported to have malignancies of the haematopoietic and reticuloendothelial system in 2014. [Acute Lymphoblastic Leukaemia (ALL) accounts for approximately 15% of these malignancies.(1) The majority of these are children.

In Sri Lanka, ALL patients are managed without Haematopoietic Stem Cell Transplant (HSCT) due to the unavailability of transplant facilities. Neither cytogenetic or molecular genetic studies for risk stratification nor molecular genetic minimal residual disease (MRD) assessments are freely available. Response to treatment is therefore solely assessed morphologically with bone marrow aspiration and trephine biopsy. Due to the lack of isolation facilities with laminar air flow ventilation, neutropenic patients during remission induction chemotherapy are managed in a common ward set up with the other oncology patients. Intensive care facilities are also limited.

Studies on CR rates, complications and survival rates of adult ALL patients through the remission induction phase of chemotherapy is lacking in this setting. There is no data on the rates of morphological clearance of blasts in bone marrow at different points of remission induction.

Objectives

This study was intended to describe the demographic and clinical features of adult ALL patients presenting to the institute, the rates of known risk factors, the basic haematological, immunophenotypic and cytogenetic (where available) characteristics, the IM, CR rates at day 8 and at the end of remission induction phase I and II, the proportion of patients with an early clearance of bone marrow blasts, the two-year DFS, OS at 2 years and to explore the association between OS and known prognostic factors including early clearance of blasts.

Literature review

Malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites result in ALL. The incidence of ALL shows a bimodal distribution with more than 80% of cases occurring in the paediatric population and the second peak seen among adults around 50 years of age.(2) While the outcome of paediatric patients is a success story, the prognosis for the elderly is poor, only 30–40% adult ALL patients achieving long-term remission despite the fact that up to 90% achieves CR.(3)

Population-based studies have shown that the median age of onset is 54 years with no gender difference.(4) Extramedullary involvement in ALL can lead to lymphadenopathy, splenomegaly or hepatomegaly in 20% of patients. CNS involvement at diagnosis is seen in 5–8% of patients. In adults, B-ALL accounts for approximately 75% of cases while T-ALL comprises the rest.(5)

The major prognostic factors for survival in adult ALL include age, white blood cell (WBC) count, cytogenetic abnormalities, immunologic subtype, the presence of a matched sibling donor, time to achieve CR and the presence or absence of molecular MRD. Determination of these factors is crucial for adapting post-remission therapy.(6)

MRC UKALL XII trial found, in Ph-negative cases, that there is a significant difference in disease-free (DFS) and overall survival (OS) based on age using a cut-off of 35. It also showed that an elevated WBC count at diagnosis, defined as above $30x10^9$ for B-ALL or above $100x10^9$ for T-ALL, was an independent prognostic factor for DFS and OS.(7)

Although earlier studies showed immunophenotype to be an independent risk factor, the latest studies have proven this to be wrong.(8) In adult ALL studies, gender as a prognostic factor has generated confusing results.(7) Central nervous system (CNS) involvement at diagnosis is historically known as a poor prognostic factor, however, with effective CNS directed therapy, the prognostic impact of this is at least partially ameliorated.(6)

Cytogenetic abnormalities have climbed up to the top of the prognostic factor list for ALL. While t(9;22), t(4;11), t(8;14), low hypodiploidy (30–39 chromosomes)/near triploidy (60–78 chromosomes) and complex karyotype (5 or more chromosomal abnormalities) carry a poor prognosis, high hyperdiploidy and del(9q) have shown a better prognosis.(9)

Achievement of CR within 4 weeks of therapy has been a well-known prognostic factor for adult ALL.(10) However, the MRC UKALL XII trial failed to show any prognostic significance as to whether CR was achieved before or after 4 weeks. It has been shown that early clearance of leukaemic cells from blood and bone marrow is associated with improved outcome in adult ALL. (11)

The main goal of induction therapy is to achieve CR and to restore normal hematopoiesis. In the CALGB 8811 trial, a CR rate of 85% and a median survival of 36 months was achieved.(12) With modern treatment protocols, CR rates following remission induction are as high as 90% of unselected adult ALL patients.(13)

A study in a Hispanic population reported an IM of 13.4% and 64.4% of this was related to infections. (14) A Korean study showed a mortality of 5% during the first 3 months of treatment among adult patients below 60 years of age.(15)

Methods

Study Design and Setting: A prospective, observational, cohort study was carried out in all the adult oncology units at the NCIM.

Methodology: All newly diagnosed adult ALL patients above 15 years of age, admitted to NCIM during a period of 12 months from 01st of April 2016 to 31st of March 2017 were included. The

diagnosis of ALL was based on the bone marrow aspiration, trephine biopsy and flow cytometry. Patients were treated on physician's discretion. Bone marrow biopsies done on day 8 and day 29 (or on the recovery of blood counts) of remission induction were assessed to determine CR. The entire patient population was followed up until two years from the recruitment of the last patient.

Outcome measures CR was defined as bone marrow aspirate being normocellular, containing <5% blast cells and showing evidence of normal maturation of other marrow elements, or, <5% blasts with reduced cellularity if the peripheral blood count is normalizing. OS at 2 years since the completion of phase 1 remission induction was calculated.

Statistical analyses: Data was analysed using SPSS® 24. P values less than 0.05 ($P < 0.05$) were considered to be statistically significant.

Results

There were 73 patients in total. Median age at presentation was 29 years. Forty-five patients (61.6%) were below the age of 35 years and 29 (39.72%) were at or below 24 years. Forty-seven were males (64.4%). Male to female ratio was 1.8:1.

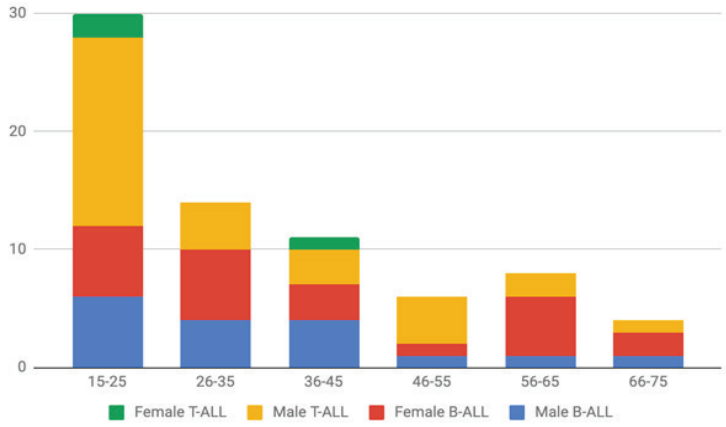

Figure 1 *Distribution of age and gender according to the phenotype*

Only 2 patients (3%) had cranial nerve palsies at the initial presentation and were diagnosed with CNS involvement.

There were 40 B-ALL patients (55%) and the remainder had T-ALL. Nine patients with B-ALL (22.5%) and 2 with T-ALL (6%) exceeded the WBC cut-offs for high risk.

Only 2 patients had Karyotyping prior to treatment. One of them had high hyperdiploidy which is prognostically good whereas the other patient had complex karyotyping which is of poor prognosis. FISH for Ph chromosome was performed only in 11 out of 40 B-ALL patients (27.5%) and it was positive in 5 patients.

Table 1 shows the numbers and percentages of patients based on the percentage of blasts in their bone marrow biopsies on day 8, day 29 and at the end of phase 2 of remission induction.

Timing of bone marrow	≤4% blasts	>4% blasts	Total	CR rate
Day 8	49	17	66	74.24%
Day 29	47	04	51	92.15%
End of Phase 2 induction	36	05	41	87.80%

Table 1

At the end of the 2 years of follow up (excluding those lost to follow up and therefore the bone marrow assessment was not performed), the OS was 35.9% and the DFS was 34.38%.

Figure 2 shows the Kaplan Meier curve for the patient population for the period of follow up (in days). The 50% survival can be estimated as 168 days from the curve.

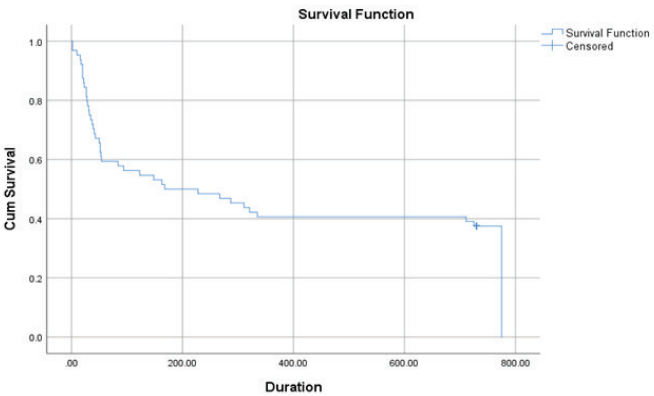

Figure 2 *Kaplan Meier curve for the 2 year follow up period*

Age ≥35 years, female gender, having a WBC count >30 at presentation in B-ALL patients seem to negatively affect the OS. However, these were not statistically significant. There were only 2 T-ALL patients with a WBC count at presentation >100. None of these 2 patient survived at the end of follow up. Risk for death was more in B-ALL than in T-ALL patients. However, the findings were also not statistically significant. OR= 1.086 (95%CI=0.387-3.049)

There was a trend towards increased mortality among patients who have not achieved an early CR at day 8 of remission induction. However, this association was not statistically significant within the 95% confidence interval. OR = 0.526 (95%CI=0.143-1.939)

None of the patients who could not achieve CR at the end of phase 1 or 2 of induction was surviving after 2 year follow up period. 69% of patients who achieved CR at phase 2 induction were surviving after 2 years.

Out of 65 patients who received induction chemotherapy 29 died at the end of induction therapy. IM was calculated to be 44.62%. The total number of deaths during the entire follow up duration was 41. Deaths during induction therapy accounted for 51.22% of the total mortality. Neutropenic fever and sepsis resulted in 62.01% (18 of 29) deaths during the induction period. Thirteen patients out of 23 who were alive at the end of 2 years of follow up period were Adolescents and Young Adults (AYAs) comprising 56.5% of the surviving population.

Discussion

This study showed a higher proportion of T-ALL patients (45.2%) than that reported in the literature (25%). It was observed that B-ALL was more common than T-ALL among females in all age groups whereas, T-ALL was more common among males particularly, between 15-25 years of age. These gender and age differences may partly be due to selection bias involved in referring patients to the institute.

Patients with Philadelphia chromosome comprises a distinct group and is the most common recurrent cytogenetic abnormality accounting for 20-30% adult B-ALL patients.(16) Patients have a poor outcome with chemotherapy alone unless they undergo allo-HSCT in first CR. With the use of Tyrosine Kinase Inhibitors (TKI) in ALL, the outcome has improved. However, as Flurosence In-Situ Hybridization (FISH) for BCR-ABL is not freely available, only 11 out of 40 B-ALL patients have been tested for this. Five patients had a positive test. As the sample size is small and because of the selection bias, this figure would not probably represent the actual situation in this population. Although TKIs are available in the public sector on a named patient basis, unavailability of FISH testing has limited the use of TKIs in ALL. This may have a profound impact on the survival of these patients. There was a trend that B-ALL fare worse than T-ALL patients although this was not statistically significant. This could probably be caused by the fact that B-ALL patients with possible undetected Ph chromosome positivity who were not treated with TKIs had a particularly poor prognosis.

Only 2 patients (2.7%) have undergone karyotyping due to the unavailability of genetic testing. This has left the treating clinicians to depend on the traditional risk stratification methods alone.

With current modern treatment protocols CR rate is around 85-90%.(17,18) This study also reported a CR rate of 92% at the end of phase 1 induction. There was a positive correlation between achieving a CR early on day 8 bone marrow biopsy (as well as on day 29 and at the end of phase 2 induction) and their prognosis. However, probably due to limited numbers of patients and the study design, a statistically significant association could not be shown.

CALGB 8811 showed a 5-year survival rate of 38%. (19) This study resulted in a 2-year survival of 36% which is comparably lower than that found in the literature. Patients were followed up only for 2 years due to time constraints in carrying out the study. However, the active treatment for ALL goes on for approximately 2.5 years. Only 7 patients had completed the full course of treatment at the end of the study period. Another 14 were still under treatment and were in CR whereas 1 patient was under treatment for relapsed disease. A longer follow up would result in more valid information on survival.

Neutropenic fever and sepsis accounted for 62.07% of deaths (18 of 29) during the first two months of treatment. The Kaplan-Meier curve (Figure 2) reached a plateau after the first year of follow up. This indicates infections as the main cause of mortality during this period. Unavailability of proper isolation facilities with laminar flow ventilation, poor diagnostic facilities with no access to PCR for atypical viruses and bacteria, extremely limited intensive care facilities with room for only 4 patients and

limited access to antifungals such as pegylated Amphotericin B among other causes might be responsible for the high mortality rate.

Conclusions

Adolescents and Young Adults (AYAs) comprise a large proportion of (40%) adult ALL patients presented to the institute and around 45% of them survived after 2 years of follow up. The proportion of T-ALL patients were higher than that reported in the literature and it exceeded that of B-ALL particularly among AYAs. Ph chromosome, a major prognostic indicator is tested only on a quarter of B-ALL patients due to unavailability of FISH testing at the institute. B-ALL patients tend to have a worse prognosis than T-ALLs probably because of the Ph-positive B-ALL patients who are left undetected and TKIs are therefore not being used, have a poor prognosis. Early CR rate on day 8 bone marrow assessment is around 74% and CR at the end of phase 1 induction therapy is around 92%. There was a trend towards a poor prognosis among patients who failed to achieve an early clearance of blasts from bone marrow which was not statistically significant. Neutropenic fever and sepsis are by far the commonest complication during remission induction. IM is 44.62% and is 5-6 times the IM reported in the developed world. Induction deaths account for 51.22% of total mortality among adult ALLs. OS and DFS at 2 years are considerably lower compared to affluent countries. Age <35, male gender, WBC count <30 in B-ALL and WBC count >100 in T-ALL had a positive correlation with survival but there was no statistical significance.

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Improving quality of life of a patient at the end of life care - Elements to be considered in a rural area

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Abstract

It is an uphill task not only to diagnose cancers at early stages but also to provide proper care to those patients throughout their entire lifetime, especially in developing countries. Improving the quality of life at the end of life can be very challenging as the dicpline is in the early stages of development in Sri Lanka.(1) Researches are yet to find out how a palliative care team alter the end of life experiences of a patient. In the interim, it is the conventional wisdom states that palliative care help to improve quality of life of patients at endo of life.

Many factors influence delivery of effective palliative care. A very well-developed health care system is essential to deliver quality care. All studies emphasizes on several factors that can bring significant beneficit to patients. Number one is fulfilling the knowledge gap in the health care staff regarding end of life care. Number two is providing adequate training to the rural practitioner to deliver end of life care. Thirdly, In adition to pain management and analgesics, all health care staff in the team should have proper education about the feeding tube, dysphagia and sputum management. Finally, home-based nursing care development will help reduce the burden on hospitals.(2)(3)(4)

Experiences and effective training on making decision about goals of care, facing challenges and approaching communication with patients and their family, interdisciplinary collaboration, withholding and withdrawing life-sustaining measures principle and practices, and dealing with cultural competency in end-of-life care would bring fruitful results in palliative care.(5)

Herewith, we discuss a patient and his family's struggles during end of life of a palliative patient. Even though the family refused curative treatment at the beginning because of multiple reasons, they wanted to give good quality of care at end of life. Unfortunately, they could not achieve what they expected. Based on patient's hospital records, perception of health care staff who were involved in patient's care and telephone conversation with a family member, three major reasons were found which were responsible for the poor quality of life at end of life.

This study analyzes three issues such as the end of life care at home related to caregiver reported outcomes, lack of rural establishment of community and family medicine with palliative centers and it's impact on quality of life and availability of morphine and other opioids in a community setting.

Keywords – supraglottic squamous cell carcinoma, patient-physician relationship, end of life care, palliative care, morphine

Background

69 year old Hindu, Tamil and married man from Vadamaraachchi developed difficulty in breathing and hoarseness of voice in 2017. After a careful evaluation, a biopsy done and confirmed that he had supraglottic squamous cell carcinoma - Stage 1. At that time, he decided not to go with disease specific treatment such as conservative laryngeal surgery or primary radiotherapy alone and chose symptomatic treatment only. A tracheostomy was placed and pain medicines were given. He was an educated person, earlier worked as a radio mechanic and had full capacity to make decisions at the time of diagnosis. Repeated counselling and family meetings did not change their mind. Even though his wife, daughter and son who had studied upto Advance Level and now married, were educated enough to understand about the prevailing situation, they refused further disease specific treatment options. They wanted to let nature of this disease take its course. Wife was the primary caretaker. They revealed that patient himself disagreed

with the active treatment as he heard about miseries suffered by people who underwent cancer specific treatment. Family members do not know the specific cancers and the treatment modalities which he talked about, but they obeyed their beloved one's wishes. Family members decided to follow with his decision because they did not interpret the situation very well despite having repeated counselling sessions. Since he was discharged from the hospital right after the tracheostomy, he was doing well except speaking difficulties because of tracheostomy. However, he was able to write and express his wishes and had good communications. His symptoms got worse in February 2019 and he was admitted to the hospital for further evaluation. At that particular time, his condition was diagnosed as advanced disease beyond cure and palliative care was recomended as that was the best option for him at that stage. The patient himself was able to communicate well, had good understanding about his conditions, coped well with the presenting situation, and recognized that he was dying. His wife was exhausted and felt depressed after taking care of him but she never hesitated tosupport him until his last breath. She was very much exhausted by travelling many hours to hospital, dealing with lack of available resources in the rural setting and giving him continuous psychological support since the beginning, all the while knowing there is no hope of curing the disease. These factors contributed to not giving proper palliative care experience for both the patient and his family. The main goals of palliation were not reached in this situation.

Challenges

1. End of life care at home – specially caregiver reported outcomes
2. Lack of rural establishment of community and family medicine with palliative centers – quality of life
3. Unavailability of morphine outside hospital setting even for palliation – symptom control

Recommendations :

End of life care at home - Caregiver outcomes and other resources

End of life care could be exhausting and place a significant burden on the family, especially who take care of them. It leads to the low quality of life for both patients and their families. In this case, patient's wife was tired of managing his needs at the end of the day and the feeling of which affected her in a negative way after during his last days and after his demise.

Having regular discussions between healthcare staff and family members, involving social workers at end of life, involving other family members in the care are some of the factors which would reduce the overall burden on an individual.

Lack of rural community and family medicine service with palliative care experience

Patient-physician relationship is a mutual professional relationship, where trust is invested between doctors and patients. In this relationship, the patient knowingly seeks the physician's assistance, and the physician knowingly accepts the person as a patient. This relationship helps to increase patient's satisfaction which would help to bring out their vulnerabilities.

As there is no well-established community and family medicine care in Sri Lanka, especially in rural areas, there was no strong rapport between patient and physician in the community setting. This led them to be in the middle of nowhere with no place to get advice unless they go to a hospital which was financially and socially very difficult for them.

Availability of Morphine

This is one of the significant issues in management of palliative care; this patient also suffered from getting morphine when they were at home.

Strong opioids like morphine and fentanyl are not widely available to use outside the hospital setting in Sri Lanka. Pros versus cons of using morphine by patients themselves are still questionable in Sri Lanka, because coping with side effects such as addiction, and respiratory depression ahave not been studied before. A proper system is needed to implement such practices in the future.

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Ecthyma gangrenosum in a child with leukemia

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Abstract

'Ecthyma gangrenosum' is a dermatological manifestation of *Pseudomonas aeruginosa* and less commonly from various other bacterial, viral and fungal infections in immunosuppressed patients. Here, we present a case of a twelve year old girl who was on active treatment for acute lymphoblastic leukemia, presenting with blisters surrounded by erythema and found to have bacteremia with *Pseudomonas aeruginosa*. She was treated as for disseminated *Pseudomonas aeruginosa* infection with anti-pseudomonal antibiotics and other supportive care. She improved with three weeks of antibiotic therapy and surgical debridement of facial and thigh lesions followed by which, chemotherapy was recommenced.

Introduction

Ecthyma gangrenosum is a characteristic manifestation of *Pseudomonas aeruginosa* bacteremia among immunocompromised patients, especially in those with neutropenia[1]. It is a rare, yet a life threatening complication which is rapidly progressive. Immunocompetent patients also can get the lesions less frequently yet; an evaluation of immune system is warranted in those patients to exclude any underlying undetected immunodeficiency.

Case report

A twelve year old girl recently diagnosed with acute lymphoblastic leukaemia(on augmented BFM consolidation chemotherapy phase of UKALL 2011 protocol) with an absolute neutrophil count of zero, presented with fever, low systolic blood pressure, bilateral cheek swelling and three skin lesions in her body (right thigh, bilateral calves). Lesions began as red macules, progressing to vesicles surrounded by a rim of erythema. The patient had mild mucositis on buccal mucosa.

Cultures from blister fluid aspirate and peripheral blood revealed *Pseudomonas aeruginosa* (Vitek 2) which was sensitive to routine anti-pseudomonas antibiotics. Fungal blood culture and Gram stain and culture of blister fluid did not yield any fungal growth.

The patient was empirically started on broad spectrum antibiotics [Intravenous (IV) meropenem and vancomycin] and antifungals (IV amphotericin) which later converted to targeted therapy (IV meropenem and amikacin). Her neutropenia was corrected by administering Granulocyte Colony Stimulating Factor (G-CSF) and buffy coat. After two weeks of therapy with above antibiotics, fever responded. Treatment was converted to IV piperacillin tazobactam. Antibiotics were given for a total of three weeks for which, the patient responded very well. The necrotic lesions on face and thigh needed surgical debridement. Chemotherapy, which was withheld on presentation, was recommenced after 14 days.

Discussion

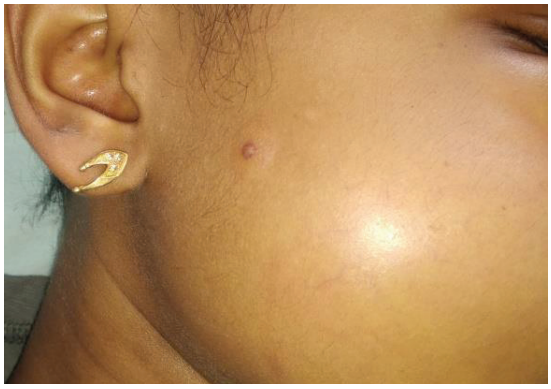
Ecthyma gangrenosum is a characteristic lesion of bacteremia with *Pseudomonas aeruginosa* in immunocompromised patients and also to a fewer percentage in immunocompetent people as well. All body parts can be affected, buttocks and groin being common sites. Facial involvement is a rare occurrence[3].

Even though primary skin lesions without any bacteremia do occur, the typical lesion is usually due to haematogenous dissemination[3].The characteristic lesion/s begin as a painless red macule which evolves into a vesicle and then to a bullae or pustule. The necrotic part in the middle later turns into a grey-black eschar surrounded by a rim of erythema[1]. The histopathology behind the characteristic lesion is toxin mediated perivascular bacterial invasion of the arteries and veins with secondary ischemic necrosis[4].

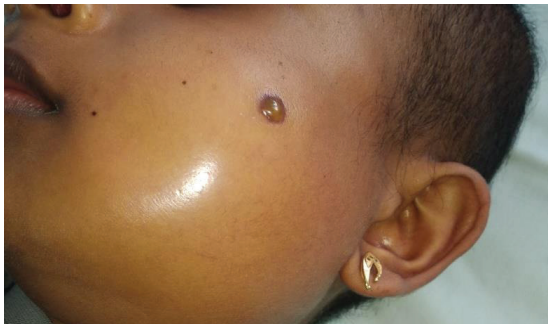
In the presence of bacteremia, the organism can be isolated from blister fluid or skin biopsy specimens as well as from blood. The initial choice of antibiotics should be based on local and institutional sensitivity patterns and targeted therapy is guided with antibiotic sensitivity of the

isolate concerned[2].The isolate in this patient was sensitive to all the antibiotics in the Pseudomonas panel which includes β lactam antibiotics such as broad spectrum penicillins, third and fourth generation cephalosporins, carbapenems, aminoglycosides and quinolones. This patient was treated with combination regimen of meropenem and amikacin. Surgical debridement also has a place if clinically indicated.[3].

This clinical entity has a high mortality rate and the prognosis depends on host's level of immunosuppression[2].



(A)



(B)

Figure 1: *Ecthyma gangrenosum lesions on face on Day 2 of admission with bilateral cheek swelling. (A) An early lesion; red macule (B) A pustule*

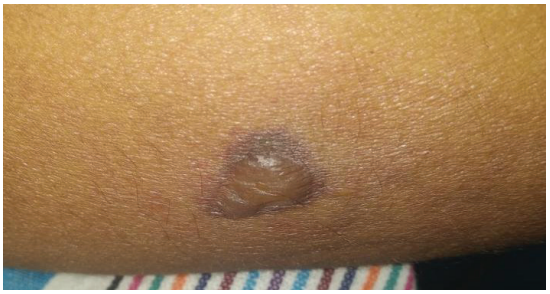


Figure 2: *Progression of ecthyma gangrenosum lesion on left thigh with central bullae and erythematous rim*

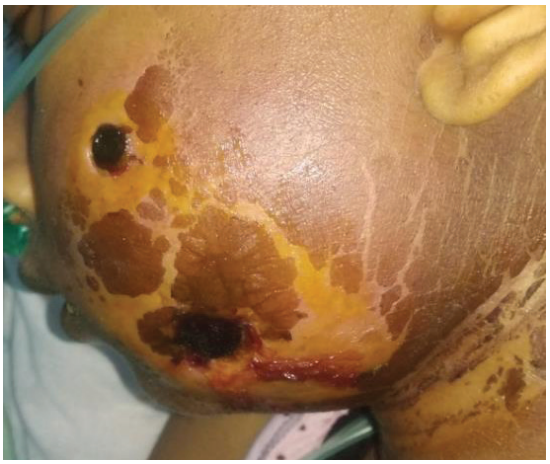


Figure 3 : *Progression of pustule on left check to eshcar*

In conclusion, clinicians, especially those who treat immunosuppressed patients, should have a high clinical suspicion to detect characteristic ecthyma gangrenosum lesions because it is a life threatening condition where early targeted treatment is life saving.

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Unexplained acute bleeding in chronic phase of chronic myeloid leukaemia due to acquired factor X111 deficiency induced hyperfibrinolysis – Experience at National Hospital of Sri Lanka, Colombo – 03 case reports

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Key words: Factor X[111] deficiency, Unexplainable acute bleeding, CML chronic phase, Chronic myeloid leukaemia

Introduction

Chronic myeloid leukaemia (CML) is a common myeloproliferative neoplasm, comprises approximately 15% of all leukaemia with an incidence of 1-2 cases per 100000 adults [1,2]. It is characterized by fusion of the Abelson murine (ABL1) gene on chromosome 9 at break point cluster region (BCR) gene on chromosome 22. This results in expression of BCR-ABL1 oncoprotein which constitutively activate tyrosine kinase that promotes growth and replication of leucocytes causing leukaemogenesis. [1]The natural course of chronic myeloid leukaemia (CML) is defined in three phases, the accelerated and blast phases that contain higher blast count and bleeding in these phases could occur due to bone marrow infiltration and thrombocytopenia. Bleeding in chronic phase with < 05 % blast count is rare, and if occurs, it is described as a part of disseminated intravascular coagulation or platelet function defect[5,8,9]. We report three cases of CML in chronic phase presented with unexplained acute bleeding due to isolated factor X111 deficiency induced hyperfibrinolysis. Bleeding due to acquired deficiency of isolated coagulation factors has been reported rarely in chronic phase of CML. The management of these acute bleeding episodes depended on specific coagulation factor replacement and targeted therapy for CML with tyrosine kinase inhibitors.

Clinical Reports

Case 1

A 49 years old man presented with spontaneous intramuscular haematoma of right forearm for 04 days duration with pallor, massive splenomegaly (18 cm) and mild hepatomegaly on examination. He neither had bleeding manifestations in the past nor family history of bleeding disorders. He had under gone uneventful dental extractions twice during last 10 years and was not on any medication.

Haematological investigations revealed severe leukocytosis 116 x 103/ µl (4 – 10 x 103/ µl) and a complete left shift of granulocytes with 01 % blast count in the peripheral blood. BCR-ABL1, p210 translocation was positive and of low risk category according to Sokal score. Haemoglobin level was 6.9 g / dl and the platelet count was 106 x 103/ µl (150 - 400 x 103 µl).

The primary coagulation tests were normal. Prothrombin time (PT) was 13.6 seconds (9 - 13 seconds). Activated partial thromboplastin time (APTT) was 30.9 seconds (23 - 37 seconds) and thrombin time was 17 seconds (15 - 19 seconds). Rotational thromboelastometry (ROTEM) revealed higher maximum lysis (ML) at both extem (48 %)and intem (34 %) and normal aptem indicating hyperfibrinolysis. (figure 1) The clot solubility test was negative but the specific factor X111 assay was 13 % (50 – 150 %). Von willibrand factor antigen, recof factor activity (vW profile), clauss fibrinogen activity and D dimer levels were normal. Liver and renal functions were normal too.

The clinical history and the results of investigations together confirmed the diagnosis of acquired factor X111 deficiency, hyperfibrinolysis and CML in chronic phase.

The acute bleeding was immediately managed

by 02 pools of cryoprecipitate transfusion and subsequent ROTEM test showed a normal coagulation status. A definitive therapy of 400 mg / daily dose of imatinib mesylate was started for CML with regular monitoring of blood counts. He achieved a complete haematological and cytogenetic remissions in 3 months and 6 months respectively and did not manifest bleeding during treatment. He had transformed in to blast phase at 10 months of his follow up.

Case 2

A 39 years old previously healthy man had undergone a bone marrow biopsy for investigations of high white cell count 453 x 103/ µl and a massive splenomegaly (20 cm). He developed multiple buttock haematoma at the site of the biopsy 02 hours after procedure followed by another 02 large haematomas on the other buttock next day. He had no past or family history of bleeding and was not on any medication. Blood picture, bone marrow findings and positive BCRABL1 translocation confirmed CML in chronic phase (blast count was 03 %)– Sokal score is of low risk category. Platelet count was 218 x 103/ µl and haemoglobin was 8.3 g / dl.

Primary coagulation investigations were normal. PT was 16 seconds, APTT 36.9 seconds and TT was 19 seconds. ROTEM test revealed a prolonged ML, 30 % in extem and 26 % in intem and normal aptem indicating hyperfibrinolysis (figure 2). Factor X111 deficiency was confirmed by 34 % plasma factor X111 level. The clot solubility test was negative. D dimer, plasma fibrinogen level, and vW profile were normal. Liver and renal function tests were normal. Factor X111 deficiency induced hyperfibrinolysis in chronic phase of CML was diagnosed.

The bleeding settled without any need of component transfusion after starting 400 mg / daily dose of imatinib mesylate therapy and subsequent ROTEM studies revealed normal coagulation. He achieved a haematological remission after 3 months of therapy but gradually deteriorated with cytopenia and transformed in to blast phase in about another 3 months.

Case 3

A 53 years old previously healthy woman had undergone bone marrow biopsy to investigate fever with high white cell count 214 x 103/ µl and moderate hepatosplenomegaly. She developed a buttock haematoma at the site of biopsy about 02 hours after the procedure followed by formation of psoas haematoma same side. She had no past or family history of bleeding and not on any medication. The blood picture, bone marrow findings and positive BCR-ABL1 p210 confirmed CML in chronic phase.

Coagulation investigations revealed normal PT 10.6 seconds, APTT 31.4 seconds and TT 12.8 seconds. Prolonged ML in both extem (31 %) and intem (28 %) with normal aptem (figure 3) and 42 % plasma factor X111 level confirmed factor X111 deficiency with hyperfibrinolysis. Clot solubility test was negative, plasma fibrinogen, D dimer levels and vW profile were normal. Liver and renal function tests were also normal. Acute bleeding had settled after starting 400 mg / daily dose of imatinib mesylate without any need of component transfusion and subsequent ROTEM tests indicated normal coagulation status. She achieved complete haematolgical response in 3 months and major molecular response in 1 year.

Discussion

Incidence of bleeding in CML is reported to be the lowest among myeloproliferative disorders (29 %)[5]. Bleeding diathesis in accelerated and blast phases of CML is mainly due to bone marrow infiltration, severe thrombocytopenia or global consumptive coagulopathy driven by cytokine secreting blasts. Platelet dysfunction or disseminated intravascular coagulation is described as possible causes of rare occurrence of bleeding in the chronic phase[5]. However acute incidence of bleeding in the chronic phase of CML due to acquired, isolated coagulation factor X111 deficiency is extremely rare[16].

The pathophysiological mechanism behind isolated factor X111 deficiency could be multifactorial but not exactly known. Hypothetically it might be due to consumption or high turnover of coagulation factors by large masses of circulating leukocytes and quantitative or qualitative defects of coagulation factor X111 in plasma due to development of inhibitory antibodies.

In most of the cases acquired factor X111 deficiency is partial and does not lead to significant bleeding as 2 - 3 % plasma factor X111 level is adequate to maintain haemostasis. On the other hand, diagnosis of factor X111 deficiency is a challenging task as the screening test for factor X111 deficiency is less sensitive (< 5 %)[14] while the routine coagulation test results remain within normal limits. A high index of clinical suspicion and specialized laboratory tests such as ROTEM test and plasma factor X111 assay are important

in the diagnosis.

Unexplainable episodes of acute bleeding manifestations in patients with haematological malignancies, with high cell turnover should be evaluated beyond first level haemostatic investigations for exact diagnosis of the coagulation defect to prevent its impact on morbidity and mortality. The management of such acquired coagulopathy depends on specific treatment of the coagulopathy and concurrent targeted therapy for the malignancy.

As a note of observation, two out of these three patients with CML in chronic phase who developed bleeding due to acquired factor X111 deficiency had transformed in to more aggressive phase of the disease while on therapy.

Conclusion

Acute bleeding is rare in chronic phase of CML. Acquired deficiency of isolated plasma factor X111 induced hyperfibrinolysis was diagnosed in unexplained episodes of acute bleeding occurred in the three patients we evaluated during the chronic phase of the disease. Such bleeding manifestations are linked to high impact of morbidity and mortality unless the diagnosis of specific acquired coagulopathy was assessed beyond first level coagulation investigations. The management of acquired coagulopathy depends on specific plasma factor replacement and concurrent targeted therapy for CML.

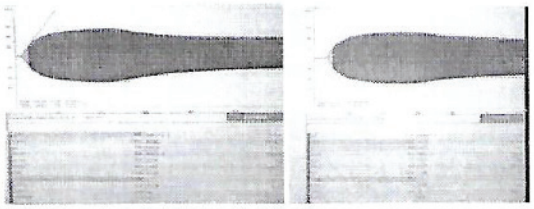

Figure 1:

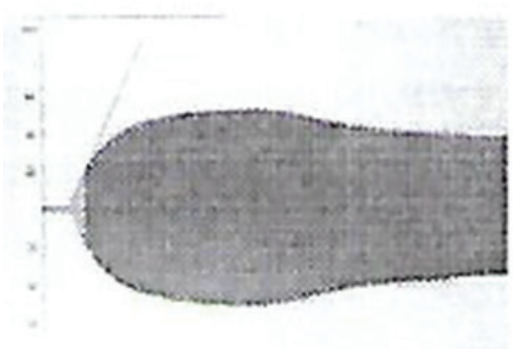

Figure 2:

Figure 3:

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