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A Study on the Assessment of Adverse Drug Reactions of Tyrosine Kinase Inhibitors and Their Impact on Quality of Life in Solid Organ Malignancy Patients

Reefath shareefa[1], Ramakrishna prudhivi[2], Chandana DB[1] , Mohammed Osama Akhtar[1], Milan Anna George[1], Shweta Srivatsa[3]

[1]*Department of Pharmacy Practice, Dayananda Sagar College of Pharmacy, Bengaluru- 560078, India.*
[2]*Department of Pharmacy Practice, Faculty of Pharmacy, Dayananda Sagar University, Bengaluru- 560078, India.*
[3]*Department of Pharmacology, Consultant Clinical Pharmacologist, Sri Shankara Cancer Hospital and Research Centre, Bengaluru-560004, India.*
**Corresponding Author: Mr. Ramakrishna Prudhivi,*

Abstract
Background: *Targeted therapy such as TKIs have prominent application in treatment of solid organ malignancies due to their effective response associated with changes in HRQoL scores during treatment and correlation of ADRs with medication adherence.*
Objectives*: The aim of the present study is to assess the Adverse Drug Reaction of Tyrosine Kinase Inhibitors and their impact on Quality of Life in Solid Organ Malignancy Patients.*
Methodology*: 33 patients with solid organ malignancies on TKIs were included in this prospective, observational and analytical study conducted in the day care wards and in-patient department of Sri Shankara Cancer Foundation Hospital and Research Centre, Bengaluru, India.*
Results*: Out of 33 volunteers, 23(69.7%) were males and 10(30.3%) were females. In addition, the highest percentage of patients with an average age group was 65.91±2.98 years. Overall 17(51.51%) had NSCLC, 12(36.36%) with HCC and 4(12.12%) patients were presented with GIST. Further 69.69% of the patients reported of having one or more ADRs. The commonly occurring ADRs were Rashes (18.60%) followed by Emesis (13.95%), Anorexia and Constipation (11.63%). The patients showed variable clinical characteristics and improved overall quality of life. The functional scales has improved except financial burden, which was increased in all solid organ malignancy subjects consequently due to the high cost of treatment. Symptoms such as dyspnoea, coughing, sore mouth, dysphagia have gradually reduced whereas haemoptysis, peripheral neuropathy fatigue, insomnia were worsened in first month but got improved by third month.*
Conclusion*: The TKIs showed minimal ADRs and significant functional improvement in health status during the course of treatment.Our findings suggest that changes in HRQoL scores from baseline during treatment, as measured on subscales of the EORTC QLQ-C30 and QLQ-LC13, HCC18 and STO22 are significant prognostic factors for survival.*
Keywords*: Tyrosine Kinase Inhibitor, Quality of Life, Solid Organ Malignancy, Adverse Drug Reactions, Non small cell lung carcinoma, Hepatocellular carcinoma, gastrointestinal stromal tumour.*

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I. Introduction

Cancer is one of the leading causes of death. Most of the tumors are caused by abnormalities in the genetic material of the transformed cells. Solid tumors are abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancerous), or malignant (cancerous). Different types of solid tumors are named for the type of cells that form them are sarcomas, carcinomas, and lymphomas.[1] Lung cancer includes two main types; Non-small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC). NSCLC begins in the epithelial cells when healthy cells in the lung change and grow out of control, forming a mass of tumor, a lesion, or a nodule. These cells can be carried away in blood or lymph that surrounds lung tissue. People with stage I NSCLC, the 5-year survival rate is about 92% to 68%, 60% to 53% in stage II, 36% to 13% in stage III and around 1% in stage IV.[2] There are 5 basic ways to treat NSCLC: Surgery, Radiation therapy, Chemotherapy, Immunotherapy and Targeted therapy.[3]

Gastrointestinal stromal tumors (GISTs) are uncommon tumors that starts in special cells called the interstitial cells of Cajal (ICCs) also called as pacemaker cells in the wall of the gastrointestinal (GI) tract or

digestive tract.[4] The most common location for GIST to develop is the stomach (50-60%), followed by the small intestine (30-40%), colon and rectum (5-10%), and oesophagus (5%).GISTs are rare, it is estimated to be roughly 10-20 per million people per year. Each year, approximately 4,000 to 6,000 adults in the United States will be diagnosed with a GIST.[5] In most GISTs the KIT gene and PDGFR gene are mutated, so the cells are always growing and dividing.[6] Treatment options and recommendations for GIST depend on several factors such as Size, Number of dividing cells, Genetic makeup and Primary location. Surgery, Pharmacological/Systemic therapy, Radiation therapy and Chemotherapy.[7]

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer caused by the growth and spread of unhealthy cells in the liver. Cancer that spreads to the liver from another organ is called metastatic liver cancer.[8] According to the available data the age adjusted incidence rate of HCC in India for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 population per year.[9] Risk factors are Male gender, race or ethnicity like people of United states, Asian Americans and pacific Islanders have highest rates of liver cancer ,chronic viral hepatitis, cirrhosis, non alcoholic fatty liver disease, primary biliary cirrhosis, inherited metabolic diseases, heavy alcohol use, obesity, type 2 DM, and certain rare diseases like tyrosinemia ,alpha 1-antitrypsin deficiency, glycogen storage disease, Wilson disease.[10] Available treatment options are Surgery (Hepatectomy), Liver transplant, Ablation therapy, Embolization therapy, Immunotherapy, Radiation therapy and Targeted therapy. [11]

Tyrosine kinases are an important target because they play an important role in the modulation of growth factor signaling in selected malignancies. Inhibitors of tyrosine kinase compete with the ATP binding site of the catalytic domain of several oncogenic tyrosine kinases. They are orally active, small molecules that have a favorable safety profile and can be easily combined with other forms of chemotherapy or radiation therapy. Several tyrosine kinase inhibitors (TKIs) have been found to have effective antitumor activity and have been approved.[12] For mutation in EGFR Erlotinib, Gefitinib, Afatinib are an initial treatment option for NSCLC. Osimertinib is also approved for the treatment of metastatic NSCLC with an EGFR mutation when the other drugs listed above no longer work. Mutations in the ALK gene are found in about 5% of patients with NSCLC then Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib are the treatment options.[13]Imatinib was the first targeted therapy approved for GIST by the U.S. Food and Drug Administration (FDA). Sunitinib is the treatment of choice for GIST when the tumor continues to grow even after treatment with imatinib. Regorafenib indicated for the treatment of locally advanced, resectable, unresectable or metastatic GIST in patients who have been previously treated with imatinib and sunitinib. Larotrectinib is an NTRK inhibitor.[14] Targeted therapy such as Sorafenib, Lenvatinib, Regorafenib, Cabozantinib is a treatment that uses drugs or other substances to identify and attack specific HCC cells without harming normal cells.[15]

Adverse drug reactions (ADRs) are those unwanted drug effects that have considerable economic as well as clinical costs as they often lead to hospital admission, prolongation of hospital stays and emergency department visits.[16] The WHO has defined ADR as "any response to a drug which is noxious, unintended, and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of a disease or for the modification of physiological functions.[17] Adverse drug events of TKIs include gastrointestinal symptoms, arthralgia/myalgia, rash, fatigue, and myelosuppression. Intolerance also occurs with the second-generation TKIs such as dasatinib and nilotinib. Thus, safety and tolerability of each TKI may influence treatment selection.[18] The most common side effects are skin changes, weakness, diarrhea, and hepatotoxicity. The majorities of the side effects are observed in a mild or moderate grade and are reversible. A rare but potentially fatal side effect of TKI therapy is interstitial lung disease (ILD).Hematologic toxicities such as myelosuppression is most common ADR from TKIs.[19] Hence the ADR burden due to the above mentioned risks becomes an important matter of study and vigilance among the healthcare practitioners actively involved in the effective treatment of oncogenesis and tumor genesis. [20]

The term quality of life (QoL) is used to evaluate the general well-being of individuals and societies. WHO defined QoL as "an individuals' perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment.[21] Health-related quality of life (HRQOL) covers the subjective perceptions of the positive and negative aspects of cancer patient's symptoms, including physical, emotional, social, and cognitive functions and, importantly, disease symptoms and side effects of treatment.[22] The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) is an integrated system for assessing the quality of life (QoL) of cancer patients participating in clinical trials and other types of research in which patient-reported outcomes are collected. The EORTC QLQ-C30 version 3.0 is designed for use with a wide range of cancer patient populations, and is intended to be supplemented by tumor-specific questionnaire modules or supplements.[23]

The main aims of this study are to determine common ADRs caused due to TKIs in solid organ malignancies and their impact on QOL. Secondary aim is to record and assess the severity and causality of adverse drug reactions of TKIs.

II. Methodology

Study site: The study was carried out in the Inpatient Department and day care wards of Sri Shankara Cancer Foundation Hospital and Research Centre, Basavanagudi, Bengaluru.

Design of the study: The study was a prospective observational and analytical study with sample size of 33 volunteers.

Inclusion criteria and Exclusion criteria:

The study was conducted for a period of 6 months (September 2018 – February 2019). All the patients either sex who are diagnosed with solid organ malignancy or prescribed with TKI were included. A total number of 50 patients gave consent for the study. But 17 patients were excluded as patients who were not willing to participate in the study and whose data was incomplete, patients on TKI for Chronic Myeloid Leukaemia (CML).

Collection of data and Study procedure

The patient was chosen based on inclusion and exclusion criteria and details of the patient such as patient demographics, demographics, risk factors, clinical and biochemical characteristics, procedures and investigations performed during the hospital stay, specific issues related to tyrosine kinase inhibitor were collected in specially designed patient profile form.. The patient was asked for predictable and non-predictable ADR when they are on TKI therapy.

A) ADR Assessment: Naranjo Probability scale was used to assess the Causality of ADR, Hart wig severity assessment scale was used to assess the severity of ADRs and Schumock and Thornton was used to assess the Preventability of ADRs.

B) QOL Assessment: The data of QOL was collected thrice i.e., at baseline, after a month and after three months of TKI therapy. There are specially designed scales for measuring the QOL in various cancer types.

i) EORTC QLQ-C30(Version 3.0)

The QLQ-C30 questionnaire consists of 30 questions (items measuring physical and mental and mental health status). In 1980, the EORTC created the Quality of Life Group, which in 1986 initiated a research program to develop an integrated, modular approach for evaluating the QoL of patients participating in cancer clinical trials. This led to the development of the EORTC QLQ-C30, a quality of life instrument for cancer patients. The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.[24]

General principles and scoring of EORTC QLQ-C30(Version 3.0)

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items.

Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases:

- Estimate the average of the items that contribute to the scale; this is the raw score.
    - Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

ii) EORTC QLQ-LC13 (LUNG CANCER)

In clinical research, the LC13 is considered a standard instrument for measuring the quality of life of patients with lung cancer. The QLQ-LC13 includes questions assessing lung cancer-associated symptoms (cough, haemoptysis, dyspnoea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The International Consortium for Health Outcomes Measurement has chosen the EORTC QLQ -C30 and the LC13 as tools for scoring reported outcomes as indicators for lung cancer.

Scoring of QLQ-LC13

The lung cancer module incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis. The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single items of the QLQ-C30.[25]

iii) EORTC QLQ-HCC18 (Hepatocellular Carcinoma)

The QLQ-HCC18 consists of 18 questions, conceptualized as consisting of 6 scales and 2 single items. It should always be complemented by the QLQ -C30.Developed in 2004 by European Organization for Research and Treatment of Cancer contains six multi -items scales addressing fatigue, body image, jaundice, nutrition, pain and fever, as well as two single item addressing sexual life and abdominal swelling. The scoring is same as that of EORTC QLQ -C30. [26]

iv) EORTC QLQ -STO22(Gastric cancer module)

The QLQ-STO22 includes 22 items concerning disease and treatment-related symptoms and side effects, dysphagia, nutritional aspects and items about the emotional problems of gastric cancer. The module has been developed according to the guidelines, and approved after formal review. The scoring is same as that of EORTC QLQ -C30. [27]

Analysis of data

Data were recorded on a pre-designed data collection form and managed on an MS Office Excel spread sheet. The descriptive statistics were represented by mean ± standard deviation and percentages. The differences between the groups were determined by the parametric t-test & non-parametric statistical test: ANOVA tests wherever appropriate. Graph Pad prism-5 statistical software was used for the data analysis. Statistical significance was defined as $p<0.05$. All P values were two tailed.

Ethical clearance

The study protocol was prepared and submitted to Sri Shankara Cancer Foundation Hospital and Research Centre for ethics committee on human subject research for ethical clearance. The study was approved by Institutional Ethics Committee and issued ethical clearance certificate (SSHRC/IEC7/40) for the same.

III. Results

Results were based on 33 patients receiving treatment for Solid organ malignancies. Among 50 patients, as per inclusion and exclusion criteria, 33 patients were enrolled in the study and followed up to three months for the completion of the study.

The study results showed that 69.69% of the patients were male and 30.30% were female. Age-wise distribution of the patients were analysed and it was found that majority of patients (39.39%) belongs to the age group of 61-70 years. Among 33 patients diagnosed with Solid Organ Malignancy, the maximum number of patients were diagnosed with NSCLC (51.51%) followed by HCC (36.36%) and GIST (12.12%) On analysing co-morbidities of study population, it was noted that 45.45% were affected with Diabetes Mellitus followed by Hypertension (33.33%), Hypothyroidism (12.12%) and IHD (9.09%). In NSCLC Gefitinib is more frequently prescribed (23.52%) followed by Erlotinib (17.64%) and Crizotinib (11.75%). Other drugs like Afatinib, Imatinib, Nintedinib, Sunitinib, Ceritinib, Axitinib, Lorlatinib, and Lenvatinib are less frequently prescribed. In HCC Sorafenib (71.42%) is more commonly prescribed TKI than Lenvatinib (28.57%). In GIST Imatinib is the only prescribed TKI as mentioned Table1.

A total 12 different types of ADRs were observed among 23 (69.69%) patients, who resulted in one or more ADRs and the total number of ADRs were 43 as shown in Figure 1. Out of 12 different types of ADRs the most frequently occurring ADR was Rashes (n=8, 18.6%) followed by Emesis (n=6, 13.95%), Anorexia (n=5, 11.63%) and constipation (n=5, 11.63%). Gastrointestinal ADRs were highest in number followed by the hypersensitivity ADRs. Gastrointestinal ADRs mainly include Emesis, Anorexia, Constipation, Diarrhoea and Mouth sores. Table 2 showed that majority of the ADRs were possible (n= 26, 60.47%). As the ADRs had been identified, their severity level was also assessed. Majority of the patients had moderate ADR (n = 24, 55.81%). Most of the ADRs were latent. The patients were classified into three groups according to their age namely, young adults (18–35 years), middle aged adults (36–55 years) and older adults (>55 years). Figure 2 showed the incidence of ADRs with respect to age in which middle-aged adult patients had a higher incidence of ADRs (80%). A total of 13 different TKIs were prescribed for patients with solid organ malignancy out of which 10 TKIs were causing ADRs and was found that most offending TKIs are Erlotinib and Sorafenib as represented in Figure 3.

QoL scores in all patients were represented in Table 3.17 lung cancer patients had consented and completed HRQOL with EORTC QLQ-C30 questionnaire with additional specific lung cancer questionnaire

LC13. The global health status (QoL) had significantly improved from baseline to after a month (p = 0.0034**). All functional scales except EF and CF were improved from baseline to third month of TKIs treatment. But the mean scores of functional scales were significantly upgraded from baseline to third moth of TKIs treatment(p =0.0045*). The symptom scales of lung cancer patients under tyrosine kinase inhibitors shows variable clinical characteristics scales like fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP) which had gradually decreased from baseline to first month and then to third month on tyrosine kinase inhibitors and hence showed the improved quality of life, and statistically showed significant increment from one month to third month (p = 0.0350*) and more significant increment from baseline to third month (p = 0.0013**). However other scales such as constipation and diarrhoea had worsened and the patient QOL had been reduced and the last symptom scale that is financial difficulties had increased from baseline to third month. Among the symptoms scale specific to LC13, the symptoms such as Dyspnoea (LCDY), coughing (LCCO), sore mouth (LCSM), dysphagia (LCDS), alopecia (LCHR), pain in chest (LCPC), pain in arms or shoulder (LCPA), pain in other parts (LCPO) had gradually reduced from baseline to third month on tyrosine kinase inhibitors. The value of dyspnoea (DY) is indicating the increment in QOL. While other symptoms scales such as haemoptysis (LCHA), peripheral neuropathy (LCPN) had worsened from baseline to first month symptoms had reduced from first to third month The statistical analysis proved that there was significant improvement in QOL of patients on tyrosine kinase inhibitors from baseline to third month (p= 0.0082**) as shown in Table 4.

12 HCC patients who were on tyrosine kinase inhibitors assigned to complete the HRQOL EORTC QLQ C-30 and HCC 18 questionnaire. Patient characteristics at baseline in terms of global health status (QoL) was compared with 3 months after initiating tyrosine kinase inhibitors and it was observed that the QOL of patients was increased significantly from baseline to third month and was statistically proven (p <0.001***). All scores of functional scales emotional functioning (EF) increased from baseline to third month.

Symptoms such as constipation (CO) and diarrhoea (DI) whose scores had been increased when compared to baseline and the first month but significantly reduced in the third month on tyrosine kinase inhibitors whereas the financial difficulties (FI) had increased irrespectively from baseline to third month. The symptoms such as Fatigue (Fati), Body image (BI), Jaundice (Jaun), Nutrition (Nutn), Pain(Pain), Fever (Fev), Abdominal swelling (Ab) that are specific to hepatocellular carcinoma had been noticeably reduced when compared from baseline to third month and hence proved improved QOL of patients on tyrosine kinase. However the sex life (Sx) of the patients under tyrosine kinase inhibitors from baseline to third month is found to be ideal and statistically proved that there was a significant difference (p= 0.0298**) in QOL of patients taking tyrosine kinase inhibitors as shown in Table 5.

Four gastro intestinal stromal tumour patients who were on tyrosine kinase inhibitors assigned to complete the HRQOL EORTC QLQ C-30 and GIST specific questionnaire STO-22. Patient characteristics at baseline in terms of global health status was compared with 3 months after initiating tyrosine kinase inhibitors and it was observed that the QOL of patients was increased significantly from baseline to third month. The health domain scores of functional health scales also proved improved QOL of patients who were on tyrosine kinase inhibitors, when compared between baselines and third month.

The functional scales include Nausea and vomiting (NV), constipation (CO) and diarrhoea (DI) had considerably increased when compared between baseline and first month and were noticeably reduced in the third month on tyrosine kinase inhibitors(p=0.0085**).

The symptom scale specific to STO-22 such as Dysphagia (STODYS) had been constantly increased from baseline to third month, Pain (STOPAIN),Reflux symptoms (STORFX) and dry mouth (STODM) had decreased from baseline to third month. Eating restrictions (STOEAT) ,anxiety (STOANX), body image(STOBI), taste (STOTA) , hair loss (STOHL) had significantly increased from baseline to first month and these symptoms however came in check in the third month.

IV. Discussion

In this study, an attempt was made to study the Quality of Life and Adverse Drug Reactions among the solid organ malignancy patients who were prescribed Tyrosine Kinase Inhibitors. This study highlighted the importance of using specific target therapy of TKI in suitable patients.

Among the 33 patients who were involved in the study, males were more prone to pdevelopment Solid Organ Malignancy which was compared and found to be similar to the study conducted by Zang EA et al. It is believed that in females, the XX chromosomes will have double the tumour suppression factors and hence cancer development is more pronounced in males.[28]

In our study the most common age group associated with cancer was of above 60 years, this is because our cells can get damaged over time. Thus, the damage can build up as we age, and due to various other risk factors can sometimes lead to cancer.[29]

The study report revealed that 51.51% was diagnosed with NSCLC, 36.36% was diagnosed with HCC and lastly 12.12% was found to have GIST. Non-small cell lung cancer is the most common type of lung cancer, accounting for around 80% of cases which is similar to our findings.[30]

Upon analysing the prescribing pattern in NSCLC, 23.52% of the prescriptions were Gefitinib followed by Erlotinib (17.64%), Crizotinib (11.75%) and Afatinib (11.75%) similar to the retrospective cohort study conducted by Isobe H et al.[31] The prescription for HCC was Sorafenib (71.42%) and Lenvatinib (28.57%) while for the GIST it was only Imatinib.[32, 33]

In this study 70% of the patients reported of having one or more ADRs. The commonly occurring ADRs were Rashes (20%) followed by Emesis (16%), Anorexia (12%) and constipation (12%). Epidermal growth factor plays an integral role in the growth and keratinization of skin epithelium, and EGFRs are expressed within the follicular epithelium, sebaceous glands, and dermal capillaries. It is therefore not surprising that EGFR inhibition leads to a number of skin reactions. [34]

Diarrhoea (8%), Mouth sores (8%), Haemoptysis (4%) Drowsiness (4%), Dizziness (4%), Nasal bleeding (4%), Joint pain (4%), Itching (4%), were all amongst the less frequent ADRs. Patients should be advised to immediately discuss any symptoms of diarrhoea with their health care team. The diarrhoea can then be managed early and effectively, preventing dose reductions or treatment discontinuation, because diarrhoea is a common side effect of many cancer treatment regimens.[35]

It was found that male (67.44%) populations showed a higher incidence of ADRs than in female (32.55%) populations which is in contrast with the study by Kekäle et al. Several explanations were investigated. No single risk factor could be identified.[36]

When assessed for their causality based on Naranjo's Scale, 60.47% of ADRs were possible, 30.23% probable and only 9.3% was found to be highly probable After the ADRs were identified, their severity level was also assessed by using Hartwig criteria. It was noted that 55.81% of the patients had moderate ADR, 32.56% had mild where as 11.63% had severe ADR. Most of the ADRs had latent 60% onset, with only 12% acute and 28% sub acute. The findings were in conjunction with Phase II study with multi targeted receptor tyrosine kinase inhibitor (TKI) done by KD Miller et al., (2005) where the most frequently reported related adverse events of any grade include diarrhoea (32%), nausea (27%), fatigue (23%), hypertension (14%), headache (9%) and rash (5%). Laboratory data available for 37 patients showed grade 3 events of neutropenia (6 pts), thrombocytopenia (2 pts), and AST increase (1 pt.), with one grade 4 event of ALT increase. No treatment-related SAEs have been reported to date.[37]

The next portion of this study consists of analysing the functional and specific changes in the quality of life of the patients by using standardized questionnaires, which are specific to the disease conditions of the subjects under scrutiny. These questionnaires were derived and evaluated as per the guidelines by European Organization of Research and Treatment of Cancer (EORTC). Each subject had consented and completed HRQOL with EORTC QLQ-C30 questionnaire with additional specific cancer questionnaires that are LC-13, HCC-18 and STO-22 with respect to their type of solid organ malignant carcinoma.

The domain scores were obtained by three interventions to gather the baseline score at the beginning of the study and two consecutive follow-ups each at the first month and the third.

The global health status has increased significantly on tyrosine kinase inhibitors there is an increment in global health status, similarly the functional abilities such as physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning also improved QOL of patients who were on tyrosine kinase inhibitors, when compared between baseline to third month.[38]

The symptom scales of lung cancer patients under tyrosine kinase inhibitors shows variable clinical characteristics scales like fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss have gradually decreased from baseline to first and then to third month on oral tyrosine kinase inhibitors gradually and hence showed the improved quality of life. However, other symptoms such as constipation and diarrhoea when compared during the duration of the study the symptoms are worsened and the patient QOL has been compromised. Lastly, the symptom scale that is financial difficulties has increased from baseline to third month consequently.[39]

Among the symptoms specific to LC13, the symptoms such as dyspnoea, coughing, sore mouth, dysphagia, alopecia, pain in chest, pain in arms or shoulder, pain in other parts have gradually reduced from baseline to third month with tyrosine kinase inhibitors. The values of dyspnoea indicates the increment in QOL where as other symptoms scales such as haemoptysis, peripheral neuropathy have remained same.

This is found to be consistent with a study by Vera Hirsh et al., (2013) where the symptoms and quality of life was studied in advanced NSCLC using LC-13 on patients being treated with Afatinib.[40] It was found that in the adverse-event profile of Afatinib, a significantly higher proportion of Afatinib-treated patients showed worsening of diarrhoea, sore mouth, dysphagia, and appetite scores. However, compared with placebo, Afatinib significantly improved QoL assessed with the European Organisation for Research and Treatment of Cancer questionnaires.

The study also revealed that In the LUX-Lung 1 trial, the addition of Afatinib to BSC significantly improved non–small-cell lung cancer–related symptoms (cough, dyspnoea, and pain), fatigue, physical functioning, and HRQoL and significantly delayed time to deterioration of cough.[41]

Between September 2019 to February 2019, 12 HCC patients volunteered. The patient characteristics at baseline in terms of global health status after initiating tyrosine kinase inhibitors as well as QOL improved significantly from start to third month. The functional scales such as physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning has got better whereas the symptom scales like Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss showed the increment in QOL of patients on tyrosine kinase inhibitors. Other symptoms such as constipation and diarrhoea whose scores have increased when compared to baseline and the first month but significantly reduced in the third month on tyrosine kinase inhibitors. The financial difficulties have increased inevitably from baseline to third month. The symptoms such as Fatigue, Body image, Jaundice, Nutrition, Pain, Fever, Abdominal swelling that are specific to hepatocellular carcinoma have been noticeably reduced overall when compared improved QOL of patients on tyrosine kinase inhibitors, however the sex life of the patients under tyrosine kinase inhibitors from baseline to third month is reportedly unaffected. [42]

A study by Hinrichs et al., (2017) subjects showed a 12.1% decrease in global health score (GHS). Major decreases were observed for physical (−21.4%), role (−23.4%), and social (−21.5%) functioning and increases in symptom severity for fatigue (+30.1%), loss of appetite (+25.3%), pain (+19.4%). ECOG performance status >1 was associated with increased nausea/vomiting ($p = 0.002$) and decreased GHS ($p=0.01$). MELD score >10 was associated with increased fatigue ($p = 0.021$) and abdominal swelling ($p<0.001$). Our study showed an increase in symptom severity in patients with no symptoms for pain ($p=0.005$) and abdominal swelling ($p<0.001$).[43]

Gastro intestinal stomatal tumour patients who were on tyrosine kinase inhibitors assigned to complete the HRQOL EORTC QLQ C-30 and GIST specific questionnaire STO-22

Patient characteristics at baseline in terms of global health status is compared with 3 months after initiating tyrosine kinase inhibitors and it is observed that the QOL of patients is increased significantly from baseline to third month. The health domain scores of functional health scales also improved QOL of patients who were on tyrosine kinase inhibitors, when compared. The functional scales include physical functioning, cognitive functioning, social functioning and their values were increased while role functioning, emotional functioning was found to be declining. In addition, the functional scale specific to STO22 that includes body image have also showed higher values from baseline to third month.

The symptom scales of GIST patients under tyrosine kinase inhibitors shows variable clinical characteristics scales like fatigue, pain, dyspnoea, insomnia, appetite loss, have gradually decreased from baseline to first and then to third month on oral tyrosine kinase inhibitors and hence showed the improved quality of life. Nausea and vomiting, constipation and diarrhoea have considerably increased when compared between baseline and first month are noticeably reduced in third month on TKIs. Although the symptom scale specific to STO-22 such as Dysphagia have constantly increased from baseline to third month, Pain, Reflux symptoms and dry mouth have decreased from baseline to third month. Eating restrictions anxiety, taste, hair loss and financial difficulties have significantly increased from baseline to first month and these symptoms however came in check in the third month. Conversely, to our findings it was observed that in a phase-II study of a second line treatment of advanced gastric cancer HRQoL was maintained by Sunitinib treatment during the first three cycles of this study, though the domains of diarrhoea and reflux symptoms were noticeably worse compared to baseline.

Beyond cycle 3, HRQoL data were available for only <10 patients per cycle due to study discontinuations. At patients' last evaluation (end of treatment or withdrawal from the study), noticeable changes (deterioration) were observed in most scales and measures of the EORTC QLQ-C30 and QLQ-STO22 compared to the baseline. The domains for perceived financial difficulties, body image, and hair loss did not change noticeably. Analysis of the HRQoL endpoints measuring gastric cancer-related symptoms, general cancer-related symptoms, overall health status and quality of life shows that these scores were largely maintained during the first three cycles of Sunitinib treatment. Given that patients discontinued Sunitinib treatment due to insufficient clinical response, the subsequent worsening in health status was more likely due to disease progression than to drug toxicity in this single-arm study of limited sample size.[44]

V. Conclusion

Our study demonstrates that the drug utilization evaluation and identification of the potential adverse events play a key role in providing better patient care especially in the treatment of cancer. The use of targeted therapy such as TKI is quickly moving to the forefront of therapy for multiple malignancies. Although they lack the traditional adverse effects observed with cytotoxic chemotherapeutic agents, toxicity can be severe with these medications.

Many of the adverse effects are unique to the TKI utilized; however, there is much overlap of toxicities within each subclass. It is important to remember that patients may tolerate one better than they may tolerate the other as demonstrated in many of the case reports described above. Due to the frequency of adverse effects with these medications, patients need to be followed closely and educated regarding potential side effects prior to starting therapy. Quality of life data were prognostic for overall survival. Fatigue and nutrition scales were prognostic in the multivariable analyses alone and in combination with clinical parameters. The prognostic value of established scoring systems was increased by the addition of QoL data. The best prognostic power was achieved by combination of specific questionnaire modules for particular malignancies and slight modification pertaining to the patient co-operation and disease progression.

LIMITATIONS:

We conducted this study for six months. In this period we are unable to collect more cases of GIST. Studies done on impact of TKIs on patient quality of life are very few in India. We expect more studies to be done on this topic.

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ABBREVIATIONS:

ADR: Adverse Drug Reaction, EGFR: Estimated Glomerular Filtration Rate, EORTC: European Organisation for Research and Treatment of Cancer, GIST: Gastrointestinal Stromal Tumour, HCC: Hepatocellular carcinoma, HRQO: Health-Related Quality of Life, NSCLC: Non-Small-cell Lung Cancer, TKI: Tyrosine Kinase Inhibitor, WHO: World Health Organization.

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COMPETING INTERESTS:

The authors declare that they have no competing interests.

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Table 1: Sociodemographic data with clinical variables

Variable	No. of patients	Percentage (%)
Gender		
Male	23	69.69
Female	10	30.30
Age		
3-40	3	9.09
41-50	5	15.15
51-60	7	21.21
61-70	13	39.39
71-80	5	15.15
Economic Status		
UC	3	09.30
UM	13	27.90
M	12	44.18
LM	5	18.60
LC	0	0
UC	3	09.30
Education Status		
P	2	09.30
G	11	27.90
I	3	11.62
HS	10	27.90
MS	2	0
PS	5	23.25
+IL	0	0
Classification (Solid Organ Malignancy)		
NSCLC	17	51.51
HCC	12	36.36
GIST	4	12.12
Type of comorbidities		
Diabetes mellitus	15	45.45
Hypertension	11	33.33
Hypothyroidism	4	12.12
IHD	3	9.09
Prescription of TKIs for NSCLC		
Gefitinib	4	23.52
Erlotinib	3	17.64
Crizotinib	2	11.75
Afatinib	1	5.88
Imatinib	1	5.88
Nintedinib	1	5.88
Sunitinib	1	5.88
Ceritinib	1	5.88
Axitinib	1	5.88
Lorlatinib	1	5.88
Lenvatinib	1	5.88
Prescription of TKIs for HCC		
Sorafenib	10	71.42
Lenvatinib	4	28.57
Prescription of TKIs for GIST		
Imatinib	4	100

Table 2:.ADR data with clinical variables

Variable	Frequency	Percentage (%)
Type of ADRs		
Rashes	8	18.60
Emesis	6	13.95
Anorexia	5	11.63
Constipation	5	11.63
Diarrhoea	4	9.30
Itching	3	6.98
Mouth sores	3	6.98
Drowsiness	2	4.65
Dizziness	2	4.65
Nasal bleeding	2	4.65
Joint pain	2	4.65
Haemoptysis	1	2.33
Rashes	8	18.60
System organ classification		

Gastrointestinal disturbances	23	53.49
Hypersensitivity	11	25.58
Central nervous system	4	9.30
Haematological	3	6.98
Musculoskeletal	2	4.65
Gastrointestinal disturbances	23	53.49
Hypersensitivity	11	25.58
Causality Assessment		
Possible (1-4)	26	60.47
Probable (5-8)	13	30.23
Highly probable (>9)	4	9.3
Severity Assessment		
Mild	14	32.56
Moderate	24	55.81
Severe	5	11.63
Onset of ADR		
Acute	5	11.63
Sub-acute	12	27.9
Latent	26	60.47

Table 3: Quality of Life Scores

Scales	Before initiating the therapy	After one month	After 3 months
LC-13 HEALTH DOMAIN SCORE			
Global health status/QoL			
Global health status (QoL)	48.03±13.24	67.66±10.25	71.05±11.50
Functional scales			
Physical functioning (PF2)	52.94±11.25	58.82±11.18	63.12±11.12
Role functioning (RF2)	55.86±13.66	59.80±11.50	64.26±10.56
Emotional functioning (EF)	56.37±12.56	57.81±11.24	50.25±10.25
Cognitive functioning (CF)	55.88±14.23	62.47±13.25	50.23±12.26
Social functioning (SF)	47.78±13.25	55.88±14.26	58.00±14.45
Symptom scales			
Fatigue (FA)			
Nausea and vomiting (NV)	52.62±10.25	45.06±13.47	43.25±12.21
Pain (PA)	34.17±11.32	40.96±11.25	28.03±10.56
Dyspnoea (DY)	67.15±11.25	56.47±13.25	52.58±14.90
Insomnia (SL)	52.94±10.23	41.22±11.22	37.85±11.50
Appetite loss (AP)	37.84±14.00	30.59±13.25	29.80±12.56
Constipation (CO)	35.78±11.32	29.41±11.06	27.90±10.96
Diarrhoea (DI)	37.25±12.32	45.33±12.65	31.36±12.96
Financial difficulties (FI)	32.35±12.02	40.47±13.56	24.87±14.00
Symptom scale specific to LC 13	54.90±10.32	65.21±11.25	71.65±10.80
Dyspnoea(LCDY)	58.37±09.56	51.87±13.72	50.95±15.96
Coughing (LCCO)	64.70±12.25	45.10±11.74	42.89±10.28
Haemoptysis (LCHA)	25.49±11.25	30.45±10.25	20.99±12.21
Sore mouth (LCSM)	42.15±14.10	50.31±12.25	38.74±11.99
Dysphagia (LCDS)	41.17±12.47	37.06±12.56	36.55±12.96
Peripheral neuropathy (LCPN)	37.25±10.12	44.12±14.22	30.74±15.00
Alopecia (LCHR)	39.21±11.25	25.49±12.90	21.36±13.25
Pain in chest (LCPC)	43.14±8.56	36.27±10.20	34.56±11.59
Pain in arms or shoulder (LCPA)	59.80±8.45	45.10±10.25	42.36±12.25
Pain in other parts (LCPO)	79.72±11.02	54.90±11.24	50.36±11.56
HCC-18 HEALTH DOMAIN SCORE			
Global health status (QoL)	25.00±11.79	50.00±13.51	76.25±13.90
Functional scales			
Physical functioning (PF2)	43.30±12.06	56.67±12.19	69.02±12.25
Role functioning (RF2)	40.67±11.57	50.00±11.59	63.05±12.36
Emotional functioning (EF)	54.17±12.32	66.66±12.50	43.21±12.65
Cognitive functioning (CF)	56.02±08.00	62.17±10.25	69.02±11.06
Social functioning (SF)	16.67±08.57	33.33±10.14	49.25±10.56
Symptom scales		50.00±12.56	45.25±13.25
Fatigue (FA)		36.67±12.57	15.25±13.56
Nausea and vomiting (NV)	66.50±11.25	50.00±11.90	35.12±12.35
Pain (PA)	18.33±11.78	16.67±14.26	10.25±15.10
Dyspnoea (DY)	43.33±10.57	16.67±12.57	11.10±11.00
Insomnia (SL)	33.33±14.00	36.67±10.45	25.02±11.25
Appetite loss (AP)	23.33±13.56	30.67±13.50	10.25±14.00
Constipation (CO)	50.00±09.71	56.67±11.46	25.12±12.02
Diarrhoea (DI)	16.33±13.14	83.33±13.57	85.02±14.00
Financial difficulties (FI)	33.33±10.14	50.00±14.57	35.25±15.00
Symptom scale specific to HCC 18	66.67±13.14	66.66±12.00	38.23±12.25

Fatigue (Fati)	49.94±14.37	36.67±12.57	25.02±13.25
Body image (BI)	45.00±11.79	66.66±14.40	75.25±14.50
Jaundice (Jaun)	58.33±11.78	80.66±11.04	30.25±12.00
Nutrition (Nutn)	46.66±14.28	30.25±11.00	22.12±11.25
Pain (Pain)	40.00±11.00	50.00±13.56	33.25±14.25
Fever (Fev)	26.67±10.57	50.00±12.56	50.00±13.50
Single items	83.33±12.57		
Abdominal swelling (Ab)	50.00±11.71		
Sex life (Sx)			
STO-22 HEALTH DOMAIN SCORE			
Global health status (QoL)	33.21±10.23	45.02±11.02	57.02±11.50
Functional scales			
Physical functioning (PF2)	45.21±10.02	47.25±11.05	49.50±12.12
Role functioning (RF2)	65.12±08.48	70.10±09.50	75.15±10.15
Emotional functioning (EF)	42.12±11.23	35.10±11.46	28.10±11.96
Cognitive functioning (CF)	50.02±10.26	48.56±11.24	46.20±12.56
Social functioning (SF)	65.12±12.02	70.10±12.24	75.01±12.45
Symptom scales	69.25±11.26	51.45±11.05	45.25±11.56
Fatigue (FA)	38.56±10.25	60.25±10.46	30.45±10.56
Nausea and vomiting (NV)	46.02±12.27	45.10±11.28	44.12±11.31
Pain (PA)	36.20±09.56	40.10±10.12	44.20±10.16
Dyspnoea (DY)	56.21±9.58	50.12±10.01	45.21±11.02
Insomnia (SL)	60.10±11.10	65.12±11.24	54.10±11.50
Appetite loss (AP)	50.25±8.26	65.12±9.12	40.10±10.10
Constipation (CO)	45.10±9.56	60.10±10.20	35.01±11.10
Diarrhoea (DI)	50.10±13.12	60.12±14.20	40.25±14.40
Financial difficulties (FI)	41.78±14.25	45.16±14.51	49.12±15.00
Symptom scale specific to STO-22	54.12±11.21	49.21±11.30	41.21±11.45
Dysphagia (STODYS)	48.12±11.10	46.10±11.15	35.12±11.05
Pain (STOPAIN)	52.10±9.10	70.12±10.05	46.25±10.12
	54.12±9.23	70.21±10.12	43.89±11.10
Reflux symptoms (STOREX)	45.41±14.36	60.14±14.12	38.32±14.00
Eating restrictions (STOEAT)	47.96±9.65	51.45±10.05	42.01±10.12
Anxiety (STOANX)	48.10±14.01	52.10±14.26	36.85±14.50
Dry mouth (STODM)	54.12±9.23	68.21±10.12	48.89±11.10
Taste (STOTA)			
Body image(STOBI)			
Hair loss (STOHL)			

Table 4: Statistical Analysis of QoL in Lung Cancer

	Global health status (QOL)	**Paired t test**	**Functional scales**	**Paired t test**	**Symptom scale**	**Paired t test**	**Symptom scale specific to LC 13**	**Paired t test**
LC13								
Before initiating the therapy	48.03±13.24	0.0034**	53.76±12.99	0.1295 (NS)	45.00±11.44	0.3758 (NS)	49.10±10.90	0.0629 (NS)
After one month	67.66±10.25		58.95±12.28		43.85±12.32		42.06±11.93	
After one month	67.66±10.25	0.0843 (NS)	58.95±12.28	0.1462	43.85±12.32	0.0350*	42.06±11.93	0.049*
After three months	71.05±11.50		67.17±11.72		38.85±12.27		36.95±12.70	
Before initiating the therapy	48.03±13.24	0.0021***	53.76±12.99	0.0045*	45.00±11.44	0.0013**	49.10±10.90	0.0082**
After three months	71.05±11.50		67.17±11.72		38.85±12.27		36.95±12.70	

Table 5: Statistical analysis of QoL in Hepato cellular carcinoma patients

	Global health status (QOL)	**Paired t test**	**Functional scales**	**Paired t test**	**Symptom scale**	**Paired t test**	**Symptom scale specific to LC 13**	**Paired t test**
HCC-18								
Before initiating the therapy	25.00±11.78	0.2254 (NS)	42.16±10.50	0.4993 (NS)	39.01±11.92	0.1961 (NS)	49.99±12.25	0.0888 (NS)

After one month	50.00±13.51		53.76±11.33		40.81±12.53		53.86±12.71	
After one month	50.00±13.51	0.2381	53.76±11.33	0.621 (NS)	40.81±12.53	0.049*	53.86±12.71	0.036*
After three months	76.25±13.90		58.71±11.77		26.93±12.94		38.67±13.25	
Before initiating the therapy	25.00±11.78	<0.001***	42.16±10.50	0.0071 (NS)	39.01±11.92	0.0085**	49.99±12.25	0.0298**
After three months	76.25±13.90		58.71±11.77		26.93±12.94		38.67±13.25	

Figure-1: Incidences of ADR

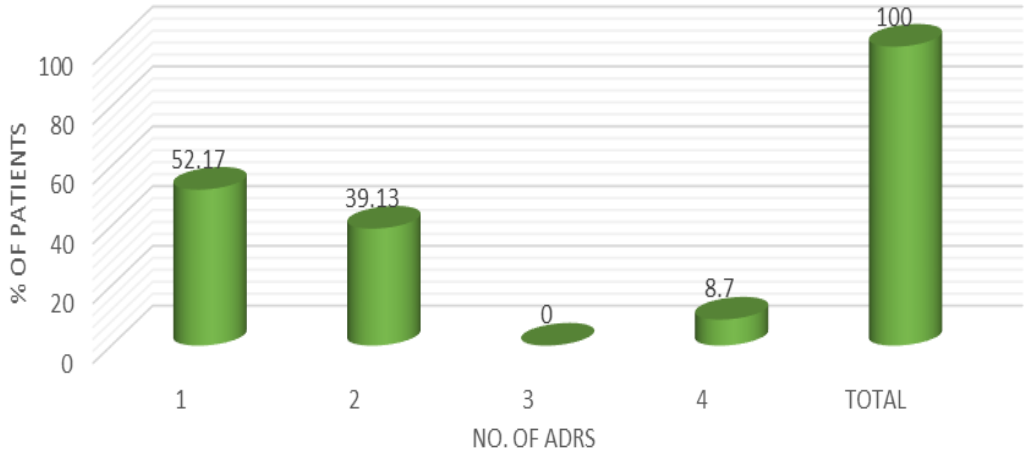


Figure-2: Incidences of ADR with respect to age

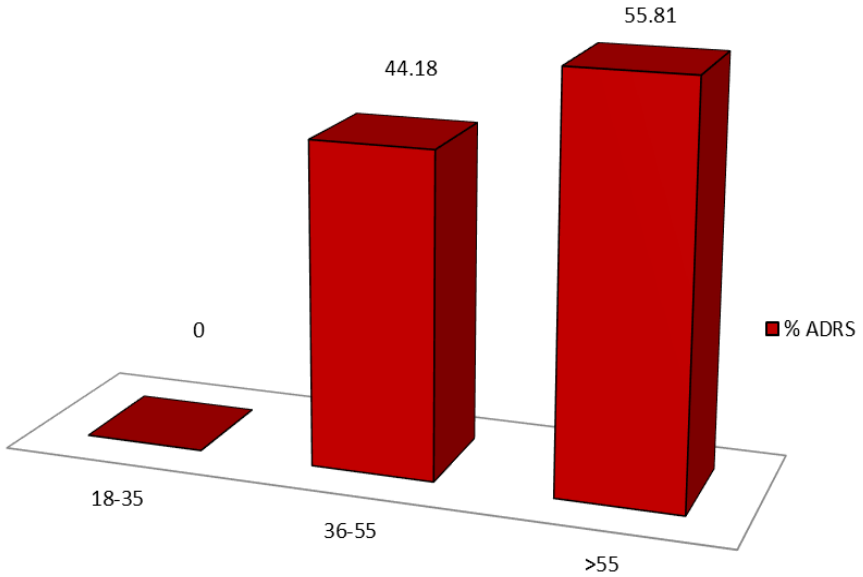
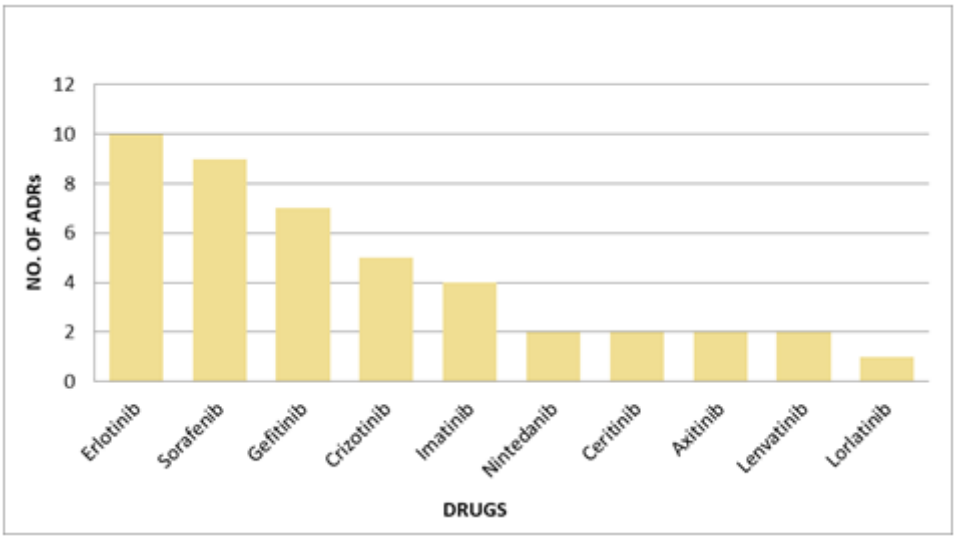


Figure-3: Drugs causing ADRs



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