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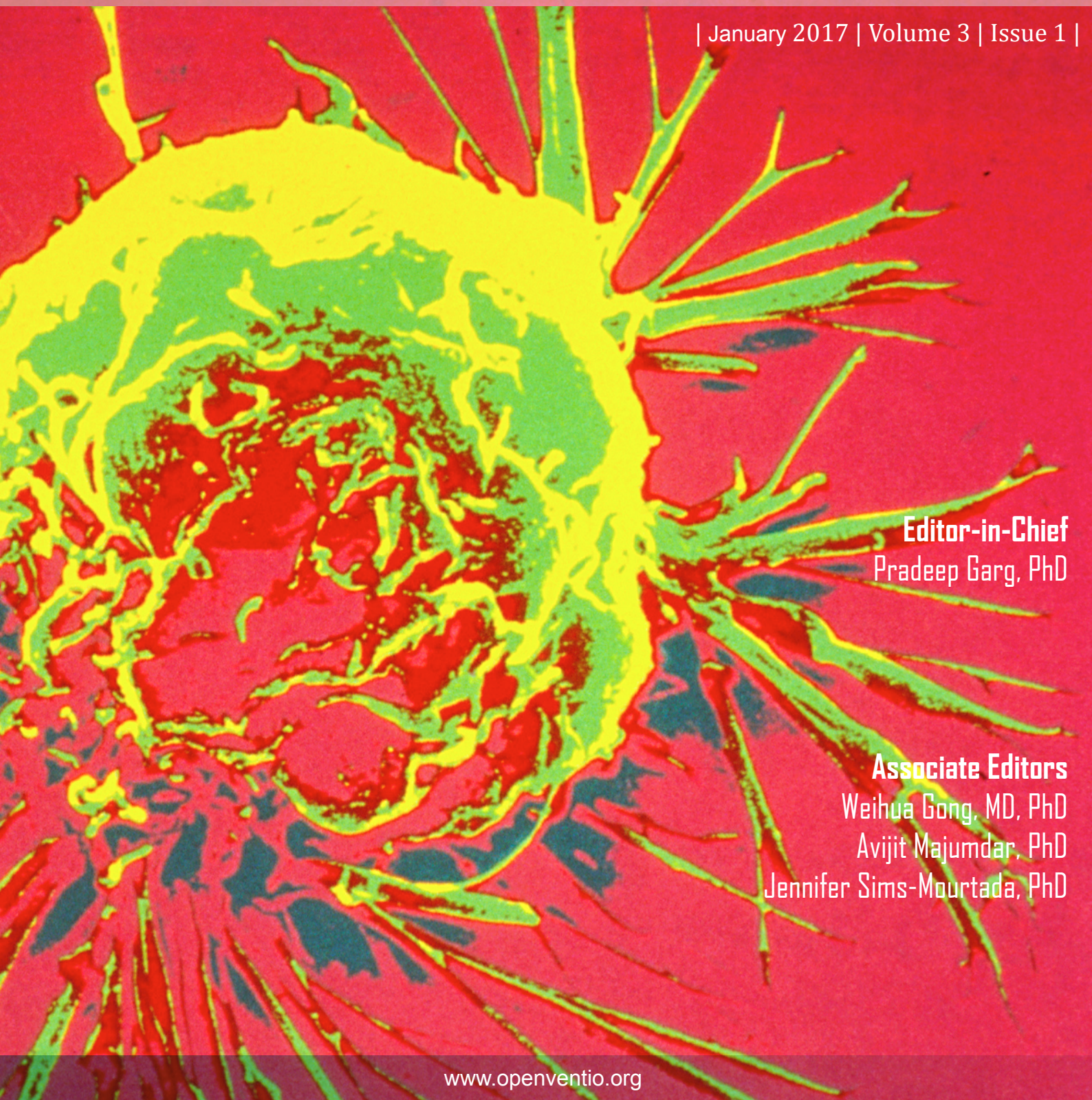
ISSN 2377-1518

CANCER STUDIES AND MOLECULAR MEDICINE

Open Journal

| January 2017 | Volume 3 | Issue 1 |



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ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-e003

Editorial

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Volume 3 : Issue 1
Article Ref. #: 1000CSMMOJ3e003

Article History
Received: September 7th, 2016
Accepted: September 8th, 2016
Published: September 14th, 2016

Citation
Mathew A, James FV. Prostate cancer trends in developing countries. *Cancer Stud Mol Med Open J*. 2016; 3(1): e1-e2. doi: 10.17140/CSMMOJ-3-e003

Prostate Cancer Trends in Developing Countries

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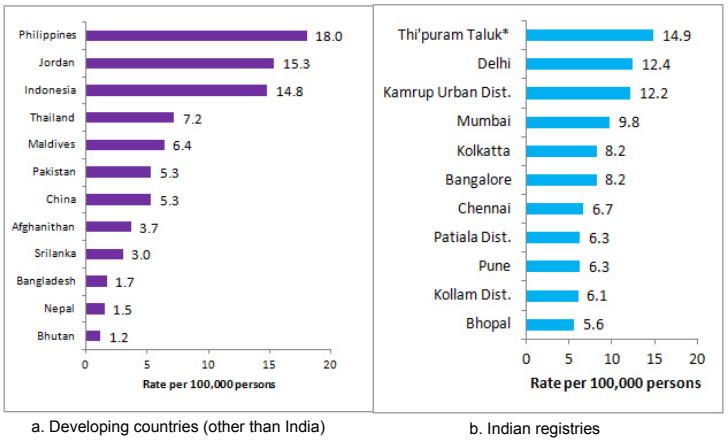
Prostate cancer is the commonest cancer in USA and most European Countries and is the 2nd commonest cancer among males globally. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men. Incidence of this disease varies more than 25-fold worldwide; the rates are highest in Australia/New Zealand and Northern America (ASR 111.6 and 97.2 per 100,000 respectively), and in Western and Northern Europe, because the practice of prostate specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions.[1]

Low incidence rates (<20 per 100,000) have been reported in most of the developing countries including India (Figures 1a and 1b). However, incidence of this disease has shown increasing trends in some developing countries.[2] A few developing countries such as Brazil, Ecuador, Costa Ricain South America, the rates are almost similar to the rates in USA (Table 1).[1] Among men residing in USA, Indians and Pakistanis have found to have increasing trend of Prostate cancer.[3] Even though, the rates are less than 10 (per 100,000) in India, increasing trends have been reported in a few areas such as Delhi, Kolkatta, Pune, and Mumbai.[4] In India, the highest rate has been observed in Trivandrum Taluk, South India (Figure 1b). In Trivandrum, it is the second common cancer among males and increasing trends in incidence has been observed (Figures 2a and 2b) (unpublished data).



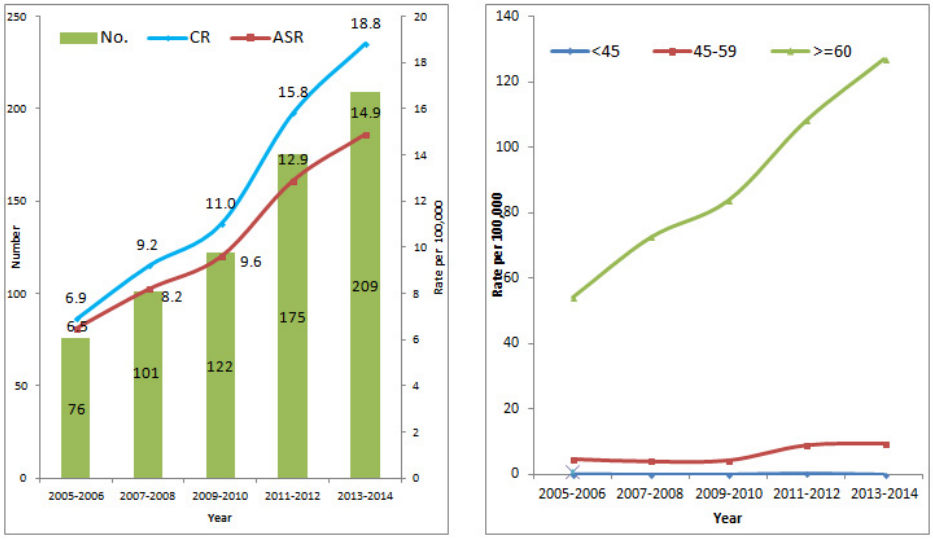
a. Developing countries (other than India) b. Indian registries

Figure 1: Age adjusted incidence rates (AARs) of Prostate cancer in Developing countries & India.

Developing countries	2003	2004	2005	2006	2007
Brazil	112.6	159.4	177.4	186.7	157.1
Colombia	72.0	64.5	63.0	69.4	66.1
Ecuador	50.3	49.4	49.1	57.7	66.4
Costa Rica	57.5	55.1	52.1	51.5	53.2
China	12.0	14.0	13.8	14.4	15.5
Thailand	6.3	5.8	6.6	5.7	6.2
Uganda	35.4	41.1	34.8	54.3	43.8

Table 1: Incidence rates (ASR) of prostate cancer in some developing countries (2003-2007).[1]

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-e003



a. #, CR & ASR b. ASpR

Figure 2: Average annual new cases (#), crude (CR) and age-standardised incidence rates (ASRs) and age specific rates (ASpR) for prostate cancer, 2005-2014, TrivandrumTaluk.
Source: Personal communication

This indicated that an epidemiologic transition in prostate cancer pattern is taking place in developing countries and are changing to more similar to "western" jurisdictions. This change is worth studying as it is a quick transition. The well known risk factor for getting prostate cancer is age.[5] There has been a steady increase in longevity of people living in this part of the country and this could partly explain the phenomenon. Also opportunistic screening by people belonging to higher economic strata leads to higher diagnosis. What would be more interesting is to learn about life-style changes particularly dietary changes occurring in developing countries as traditional food patterns could have been protective.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-e004

Editorial

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Volume 3 : Issue 1
Article Ref. #: 1000CSMMOJ3e004

Article History
Received: January 6th, 2017
Accepted: January 11th, 2017
Published: January 11th, 2017

Citation
Garg PK. Potential of molecular imaging to advance molecular medicine. *Cancer Stud Mol Med Open J*. 2017; 3(1): e3-e4. doi: 10.17140/CSMMOJ-3-e004

Potential of Molecular Imaging to Advance Molecular Medicine

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Molecular imaging is a technology that allows for non-invasive interrogation of physiological and biochemical processes in the body. Over the years, the use of Molecular Imaging is on the rise, especially towards diagnosing cancer and monitoring treatment. Molecular Imaging has a significant role to play at preclinical and translational stages in the field of Molecular Medicine. Molecular Imaging tools include Magnetic Resonance Imaging (MRI), Magnetic Resonance spectroscopy (MRS), Computed Tomography (CT), Positron Emission Tomography (PET), Ultrasound (US), and Optical Imaging among many more. While CT and MRI remains as first-line tools for diagnosing ailments by the clinicians, pre-clinical and clinical use of Positron Emission Tomography (PET) is steadily rising. Newer PET probes are being developed and being evaluated for their effectiveness in patient care and disease management. While this technology has tremendously benefitted the pre-clinical research, it has also become one of the indispensable tools in the clinic. In addition, now PET is proven to be quite helpful in expediting the drug development and discovery efforts. Over the last two decade, a significant progress is made towards expanding the role of Molecular Imaging. It plays significant role in Oncology, Neurology, ageing, drug abuse, and cardiac applications. With increased acceptance of this modality in the clinics around the world, there is a growing interest in utilizing PET to target biological systems and to assess the outcome of certain treatments in patients.

One of the early successes in PET application came from the development of F-18 labeled *fluorodeoxyglucose (F-18 FDG)*, a sugar molecule that was labeled with a short half-life PET radionuclide *Fluorine-18*. This molecule phosphorylates and subsequently traps inside the cells and thus provides a measure of glucose utilization in a given tissue. Since this principle applies to many cellular processes, the role of FDG continued to grow beyond its original oncology applications. Encouraged from initial successes with F-18 FDG, newer PET probes were developed with primary focus to target a wide array of biochemical and physiological processes. Some of the noteworthy focus areas include targeting cellular apoptosis, angiogenesis, Alzheimer's disease, dementia, moment disorders, various receptors in the brain, and numerous other biochemical pathways.

Some of the extensively explored PET probes include *F-18 Fluorothymidine (F-18 FLT)*, *F-18 Fluoromisonidazole (F-18 MISO)*, *F-18 Amyvid (F-18 AV-45)*, *F-18 FallyPride*, *C-11 Nicotine*, *C-11 Raclopride*, *O-15 Water* and scores of other probes. For example, F-18 FLT was developed as a thymidine analogue to provide a measure of thymidine uptake in tissues. This probe has been proven as a useful biomarker for assessing cell proliferation. Similarly, F-18 F-MISO was developed to assess tissue oxygenation status and has found its place in preclinical and clinical studies as tissue hypoxia marker. *O-15 water* has been applied to gather information on tissue blood flow. Dopaminergic systems are targeted using probes such as *F-18 FallyPride* and *C-11 Raclopride*. Several *F-18 fluorobenzamides* have been developed recently to target melanoma. Role of F-18 labeled testosterone derivatives is being explored to selectively target androgen receptors. These probes have shown clinical potential to target prostate cancer. Similarly radio-labeled PSMA derivatives also show significant clinical potential to target prostate cancer.

While this imaging modality is perceived as expensive and at times technically chal-

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-e004

lenging, the benefit from adopting such tools could outweigh challenges. With the backing from a large supporting literature on the usefulness of Molecular Imaging, it is prudent to engage this technology into more basic science research and in to interrogate molecular medicine paradigm. It is my hope that researchers would more aggressively incorporate Molecular Imaging techniques in their Molecular Medicine research and applications.

CANCER STUDIES AND MOLECULAR MEDICINE

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ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

Research

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Volume 3 : Issue 1
Article Ref. #: 1000CSMMOJ3114

Article History
Received: February 1st, 2016
Accepted: March 16th, 2016
Published: March 24th, 2016

Citation
Kainickal CT, Aparna MP, Ravi Kumar RK, Rafi M, Ramadas K. Current status of anti epidermal growth factor receptor therapy in the curative treatment of head and neck squamous cell carcinoma. *Cancer Stud Mol Med Open J.* 2016; 3(1): 1-6. doi: 10.17140/CSMMOJ-3-114

Current Status of Anti Epidermal Growth Factor Receptor Therapy in the Curative Treatment of Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Squamous cell carcinoma of head and neck is the most common malignancy of the upper aero digestive tract in the world. In this article, we attempt to summarize the role of anti-epidermal growth factor therapy (EGFR) in the treatment of locally advanced head and neck squamous cell carcinoma. Cetuximab plus radiotherapy is a reasonable alternative in patients who cannot tolerate standard concurrent chemoradiotherapy (CTRT). There is no benefit by adding targeted therapy in addition to standard CTRT. Trials evaluating the role of targeted agents in the adjuvant setting showed no benefit in patients with high risk features; in addition to standard post-operative CTRT. Role of adjuvant monoclonal antibody in patients with intermediate risk factors is being evaluated.

KEYWORDS: Epidermal growth factor receptor (EGFR); Head and neck-targeted therapy.

INTRODUCTION

Head and neck cancer accounts for more than 600,000 cases annually worldwide.[1] It is estimated that 57.7% of global head and neck cancers occurs in Asia.[2] Single modality treatment either surgery or radiotherapy remains the standard of care for early disease (Stage I & II). Majority of the patients with Head and Neck Squamous Cell Carcinoma (HNSCC) present at an advanced stage and requires surgery followed by adjuvant treatment or concurrent chemoradiation (CTRT).[3,4] Over a period of last two to three decades there is a paradigm shift from surgery to organ preservation strategies to improve the quality of life without compromising the overall survival.[4] Treatment regimens combining radiotherapy and chemotherapy are associated with significant acute and chronic toxicities.[5] The incorporation of induction chemotherapy prior to concurrent chemoradiation has not shown any additional benefit to CTRT alone.[6-9] These facts have led researchers to focus on a more cellular level to identify and study cellular targets which may have a role in cancer genesis and cell proliferation. Out of the various molecular markers that have been studied, Epidermal Growth Factor Receptor (EGFR) remains the most robustly studied and proven marker in head and neck cancers.

Epidermal growth factor receptor (EGFR) protein expression is detected in 90% of all HNSCC tumours.[9] EGFR is a 170-180 kd trans membrane glycoprotein tyrosine kinase receptor. It binds Epidermal growth factor (EGF), Transforming growth factor-alpha (TGF-α), and other regulating proteins. Activation of EGFR results in a complex cascade of signaling pathways that influence normal cellular proliferation and differentiation which lead to strong mitogenic activity. Ligand binding results in receptor dimerization, activation of the intrinsic kinase domain, and phosphorylation of tyrosine residues within the cytoplasmic tail. Proteins dock on the phosphorylated residues, leads to the activation of signaling pathways that promote cell growth, proliferation, differentiation, and migration.

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

High levels of EGFR protein expression is associated with decreased survival, resistance to radiotherapy, loco regional treatment failure, and increased rates of distant metastases.[10] The concept of blockade of epidermal growth factor receptor signaling pathway for anti-proliferative antitumor activity was introduced in the 1980s.[11,12] EGFR inhibitors block the EGFR phosphorylation and subsequent tumor cell proliferation.[13,14] EGFR inhibitors include monoclonal antibodies (mAb) that block the extracellular ligand-binding domain, and small molecule inhibitors (Tyrosine kinase inhibitors -TKI) that inhibit activation of the intracellular cytoplasmic tyrosine kinase.

This review article will try to enumerate the currently available clinical trial data regarding EGFR inhibitors in Head and Neck Squamous Cell Carcinoma (HNSCC), treated with curative intend. There are many monoclonal antibodies and TKIs, that have been evaluated in the treatment of HNSCC, their mechanism of action, and mode of administration is illustrated in Table 1.

ROLE OF EGFR INHIBITORS IN THE DEFINITIVE RT/CTRT SETTING

Concurrent chemoradiotherapy is the standard of care in patients with locally advanced HNSCC who are considered for non-surgical approach and is associated with increased toxicity.[5] Various phase II trials have addressed the role of EGFR inhibitors in the definitive setting along radiotherapy or concurrent chemoradiation and are summarized in Table 2.

All the phase II trials did not show any added benefit in addition to RT or CTRT except Nimozutumab. The positive

Agent	Mechanism/target/binding	Method of administration
Cetuximab	Chimeric anti-EGFR mAb	IV
Nimotuzumab	Humanized anti-EGFR mAb	IV
Panitumumab	Fully human anti-EGFR mAb	IV
Zalutumumab	Fully human anti-EGFR mAb	IV
Gefitinib	Reversible, small-molecule EGFR TKI	PO
Erlotinib	Reversible, small-molecule EGFR TKI	PO
Lapatinib	Reversible, small-molecule EGFR/ErbB2 TKI	PO
Afatinib (BIBW 2992)	Irreversible, small-molecule ErbB family inhibitor	PO
PF-00299804	Irreversible, small-molecule pan-HER TKI	PO

IV: Intra Venous; PO: Per Oral; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor

Table 1: EGFR inhibitors evaluated in head and neck cancer.

Study	Patients	Methods	Outcome	Remarks
Gefitinib[15] 2012	n=31	CTRT+Gefitinib	3-year DFS 42.9% 3-year OS 48.4%	EGFR expression did not predict for response or survival
Lapatinib[16] 2013	n=33 n=34	CTRT *vs.* CTRT+lapatinib	The median PFS 35.3 *vs.*12.1 months (p=0.18) median OS-30.9 months (p=0.382)	No difference in PFS or OS
Erlotinib[17] 2013	n=99 n=105	Elrotinib+CTRT *vs.* CTRT alone	CRR 52% *vs.* 40% No improvement in PFS (p=0.71) or OS (p=0.88)	No benefit
Nimotuzumab[18] 2014	n=23 n=23 n=23 n=23	Nimotuzumab+ CTRT *vs.* CTRT alone Nimotuzumab + RT *vs.* RT alone	Median 5-year PFS was 54.24 months (CRT+nimotuzumab) 14.95 months (CRT) (p= 0.036). 14.29 months (RT+nimotuzumab) 9.76 months (RT arms) (p= 0.41)	Targeted agents provides survival benefit to patients with inoperable advanced disease
Panitumumab[19] 2015	n=64 n=89	CTRT *vs.* CTRT+ panitumumab	PFS at 2 years 65% *vs.* 61% (p= 0·03) OS at 2 years 78% *vs.* 69% (p= 0·1.0)	No additional benefit with Panitumumab

Table 2: Anti EGFR agents tested in phase II trials along with RT/CTRT.

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

result obtained in the Nimotuzumab study needs to be validated in a phase III trial.

PHASE III TRIALS ADDRESSING THE ROLE OF EGFR INHIBITORS

Cetuximab is the first monoclonal antibody evaluated in a phase III trial in HNSCC. Concurrent cetuximab plus RT was evaluated in a multinational randomized study by Bonner et al in 424 patients with loco regionally advanced HNSCC.[20] They were randomly assigned to receive radical radiotherapy, either conventional dose or altered fractionation alone (n=213) or radiotherapy plus cetuximab (n=211). Cetuximab was given a loading dose of 400 mg/m^2 one week prior to RT, followed by 250 mg/m^2 weekly along with RT. With a median followup of 54 months, addition of cetuximab improved both loco regional control (50% *vs.* 41%, p= 0.006) and overall survival (three-year survival 55% *vs.* 45%, p= 0.03) compared with RT alone. A subset analysis conducted showed that the benefit of cetuximab plus RT was restricted to patients with a Karnofsky performance score (KPS) 90 to 100, under the age of 65 years, patients who received altered fractionation radiotherapy, and those with oropharyngeal cancer. The five year update of the trial showed sustained result and is summarized in Table 3.[21]

	RT (n=213)	RT+Cetuximab (n=211)
Median survival	29.3 months	49 months
5 yrs overall survival	36.4%	45.6%
HR-0.73, 95% CI 0.56-0.95 p=0.018		

Table 3: Five year survival data from a phase 3 randomized trial.[21]

Patients developed a characteristic cetuximab-induced acne form rash during treatment and generally resolved completely in the first weeks following the cessation of therapy. Patients with prominent rash had more than two and a half times longer overall survival than did patients with mild rash. It was explained as acne form rash is a biomarker of an immunological response and studies are conducted to identify patients who might benefit from maintenance cetuximab therapy.[21]

The major drawback of the trial was that it compared cetuximab plus RT with RT alone, which is no longer considered a standard approach for patients with loco regionally advanced disease. Another issues pointed were that different RT regimens were allowed in the trial, analysis of data were not site specific , there was lack of information regarding Quality of Life (QoL), and late complications. There is no trial directly comparing Cetuximab plus RT with concurrent chemoradiation.

The benefit of Cetuximab along with CTRT was evaluated in the randomized RTOG 0522 phase III trial.[22] In this trial, 940 patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were randomly assigned to concurrent cisplatin (100 mg/m^2 on days 1 and 22) plus accelerated RT (70 Gy in 42 fractions over six weeks) with or without concurrent cetuximab. At a median followup of 3.8 years, there was no significant difference in three-year progression-free survival, 59 *versus* 61 % (p=0.76), which was the primary endpoint of the trial.

Panitumumab, a fully humanized monoclonal antibody was evaluated in the National Cancer Institute Canada Clinical Trials Group HN.6 based on the result of subset analysis of Bonner Trial which showed benefit with altered fractionation radiotherapy with EGFR inhibitors.[23] Patients with locally advanced HNSCC were randomized to receive standard fractionation radiotherapy (70 Gy/35 over seven weeks) concurrently with cisplatin at 100 mg/m^2 intravenous (IV) for three doses on weeks one, four and seven *versus* altered fractionation radiotherapy (70 Gy/35 over six weeks) along with Panitumumab at 9 mg/kg IV for 3 doses one week prior to radiotherapy, on days 15 and 36. A total of 320 patients were recruited from December 2008 to November 2011 .With a median followup of 46.4 months, PFS of patients in the panitumab arm was not superior to chemotherapy arm (p=0.83).

In conclusion concurrent chemoradiotherapy with cisplatin remains the standard of care, for patients with locally advanced HNSCC, who can tolerate it. Patients who cannot tolerate platinum-based chemotherapy for any of a variety of reasons may benefit from the addition of cetuximab to radiotherapy. There is no added benefit for target agents in addition to standard CTRT.

In the ongoing RTOG 1016 study, patients with locally advanced p16+ oropharyngeal cancer are treated with intensity modulated radiotherapy and randomly assigned to either concurrent cetuximab (weekly)or cisplatin (on days one and 22). Results may give new insights to the inclusion of Cetuximab in the management of locally advanced p16+ oropharyngeal cancer.[24]

EGFR INHIBITORS IN ADJUVANT SETTING

Surgery followed by post-operative radiotherapy (PORT)/post-op CTRT is the standard of care in stage III/IVA patients.[25,26] Patients with intermediate risk factors like pT3-T4, pN2-N3, and nodal disease in levels IV-V, PNI+ or LVI+ merit adjuvant radiotherapy. Based on two major phase III trials, Radiation Therapy Oncology Group (RTOG) 9501 and EORTC 22931 showed additional benefit with concurrent cisplatin chemotherapy in patients with high risk features like extra capsular spread or margin positive disease. Ten-year update of the RTOG 9501 trial showed improved disease-free survival (12.3% *vs.*18.4% p=0.05), and trend towards improvement in overall survival was 19.6% *vs.* 27.1% (p=0.07), respectively in patients with high risk features.[27] EORTC 22931 showed improvement in progression free survival (47% *vs.* 36%, p=0.04) and overall survival (53% *vs.* 40%, p=0.02) and reduction in loco regional recurrences (18% *vs.* 31%, p=0.007) with concurrent cisplatin.[28] But concurrent chemotherapy was associated with more acute

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

and overall toxicity. Adjuvant chemoradiation was not tolerated by patients with advanced age, renal insufficiency, auditory dysfunction, and poor performance status. Acute toxicity [GR³3] in the RTOG study was 77% *vs.* 34% (p<0.001) and 41% *vs.* 21% in the EORTC trial (p=0.001).

A combined analysis of these trials identified patients most likely to benefit were those with positive resection margins and/or extra capsular tumor extension in cervical lymph nodes.[29]

In patients with intermediate risk group, post-operative RT alone is the usual practice, but has shown suboptimal outcome in some patients. The ongoing RTOG 0920 trial is evaluating the role of Cetuximab in addition to RT. In this trial patient with intermediate-risk HNSCC following surgery are randomized to receive standard PORT with or without cetuximab.[30]

The next question was to evaluate the role of targeted agents in high risk patients, along with post-operative CTRT. RTOG 0234 is a phase II randomized trial, in which 238 high-risk patients with SCCHN were randomly assigned to 60 Gy radiation with cetuximab once per week plus either cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2 once per week. With a median followup of 4.4 years, two year overall survival estimate was 69% (p=0.04) for the cisplatin arm, and 79% (p=0.001) for the docetaxel arm, and the 2-year disease-free survival (DFS) was 57% (p=0.05) and 66% (p=0.01), respectively.[31]

Lapatinib was tried in a phase III trial, in patients with resected stage III and IVA SCCHN. Patients with a surgical margin ≤5 mm and/or extra capsular extension were randomized to post-operative CTRT with either Placebo (P) or Lapatinib (L). RT was 66 Gy (2 Gy per day, five days per week) along with cisplatin 100 mg/m^2 of was administered on days 1, 22 and 43 of RT. P or L was given 1500 mg/day for up to one week prior to CTRT, during CTRT and for up to 12 months as monotherapy maintenance.[32] Median disease free survival (DFS) for Lapatinib was 53.6 months *versus* 54.6 months for placebo arm (2 sided p=0.45).When added to standard therapy Lapatinib, does not extend DFS, which was the endpoint of the trial.

The ongoing phase III trial-IHN01 study is evaluating the role of Nimotuzumab in the post-operative setting with CTRT in patients with high risk features.[33]

To conclude, the benefit of targeted therapy in patients with intermediate risk is being evaluated in an on-going clinical trial. Currently there is no proven benefit for targeted agents in high risk patients in addition to post-operative CTRT.

SUMMARY

Concurrent chemoradiation remains the current standard of care for treatment of locally advanced HNSCC in patients who are planned for organ preservation approach. Cetuximab along with radiotherapy may be considered as an alternative in patients who cannot tolerate cisplatin due to poor performance status and impaired renal function. Cetuximab in addition to standard chemoradiotherapy was not found to be beneficial, and is associated with increased toxicity. There is no benefit of adding targeted agents in the post-operative setting in patients who have high risk features in addition to standard adjuvant chemoradiation. RTOG 0920 is evaluating the role of cetuximab in patients with intermediate risk.

CONFLICTS OF INTEREST: None.

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ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

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CANCER STUDIES AND MOLECULAR MEDICINE

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ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-115

Observational Study

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Volume 3 : Issue 1
Article Ref. #: 1000CSMMOJ3115

Article History
Received: March 23rd, 2016
Accepted: April 20th, 2016
Published: April 26th, 2016

Citation
de Macedo JE, Lopes S, Pinho M, Santos P. Gastrointestinal stromal tumors: innovation from diagnosis to treatment based on 15 years of experience of a peripheral hospital in portugal. *Cancer Stud Mol Med Open J*. 2016; 3(1): 7-13. doi: 10.17140/CSMMOJ-3-115

Gastrointestinal Stromal Tumors: Innovation from Diagnosis to Treatment Based on 15 Years of Experience of a Peripheral Hospital in Portugal

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ABSTRACT

Aim: To investigate fifteen years of experience, in managing GISTs, according to best clinical practice, on a peripheral Portuguese Hospital. Define the behavior of GIST's and the association between the histological, immunehistochemistry characteristics and disease progression. Question if the optimal treatment was delivered in GIST patients, based on medical evidence, where limitations on evaluating molecular signatures exists.

Methods: A retrospective analysis of cases treated in Hospital of Entre Douro and Vouga from 1 January 1999 to 31 December 2014 was performed. Demographic characteristics were evaluated related to tumor characteristics according to the National Institute of Health criteria and disease progression. All patients were evaluated in a multidisciplinary team. An expert treatment decision was made according to the National Institute of Health criteria of Gastrointestinal stromal tumor's risk of recurrence after surgery. Statistical study was performed using SPSS version.

Results: Sixty-three cases were evaluated, 61.9% in female patients and 38.1% male. The median age at diagnosis was 69 years. A progressive increase in the incidence of GISTs was documented since 1999 to 2014. The most common source locations was the stomach with forty-five patients (71.4%), When assessing the Mitotic count, 27% was superior to 5 mitosis/50HPF and 73% was inferior to 5 mitosis /50HPF.

Sixty-two patients underwent surgery with R0 resection rate of 94% Immunohistochemistry was performed in all patients, and sixty-one patients were positive for CD117. Only two patients were CD117 negative. No KIT gene mutation analysis was performed.

Regarding the biological risk of recurrence or metastasis, according to the National Institute of Health, 25,4 % of the patients had a very high risk, 19,0% had an intermediate risk, 34,9% had a low risk and 20,6 % had a very low risk.

Of the 63 patients, 25.4% (n=16) were submitted to adjuvant treatment with imatinib (400 mg/daily) during 3 years. Only 7.9% (n=5) received palliative treatment with imatinib and sunitinib.

Only in 11% of the patients the disease progressed (median time to progression of 36 months). The mortality rate was 12.7% (n=8). Fifty-five patients were alive (87.3%) at the end of this retrospective study.

Conclusions: Mutation analysis was not performed, which might have influenced the treatment and prognosis. Optimize therapy based on molecular signatures are extremely important for a cost-effective treatment.

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-115

KEYWORDS: Gastrointestinal Stromal Tumors (GIST); Molecular signature; Target therapies; Innovation; Costs.

ABBREVIATIONS: PFS: Progression Free Survival; ICC: Interstitial Cells of Cajal; GIST: Gastrointestinal Stromal Tumors; E-GISTs: Extra-gastrointestinal Stromal Tumors; NF1 Neurofibromatosis type I; R0: Complete resection; R1: Microscopic disease at resection margins; HPF: High power microscope field; NIH: National Institutes of Health; DOG1: ANO 1-anoctamin 1; SMA: Smooth muscle actin; KIT: also known as CD117; PDGFRA: Platelet-derived growth factor receptor-alfa; VEGFR: Vascular endothelial growth factor; FGRF: Fibroblast growth factor receptor.

CORE TIP

We report, fifteen years of experience in managing GISTs on a peripheral Portuguese Hospital. Surgery is the gold standard therapy. But in the adjuvant setting, recent studies have shown that imatinib, a tyrosine kinase, may change the natural history in high and very high risk tumors. On the other hand, recent molecular innovation has arisen concerning molecular characterization of these tumors, with direct consequences on the appropriate targeted treatment. Besides cost-effectiveness studies approved in treating specific groups of patients, this still continues as a heavy burden for the National Health Care system.

INTRODUCTION

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal (non-epithelial) tumors of the gastrointestinal tract. They probably originate from the interstitial cells of Cajal (ICC), which are located in the myenteric plexus of the gastrointestinal tract. ICC are the pacemaker cells responsible for gut peristaltic contractions.

They represent about 1-3% of all GI tumors, most of which 60% have gastric origin, and 30% comes from the small intestine. They are less common in the colon, rectum and esophagus (>1%). In other places within the abdominal cavity they can also be found, in less than 5%, in the omentum, mesentery or the retroperitoneum, and are known as extra-gastrointestinal stromal tumors (E-GISTs).

Historically, GIST's were first described in the 1980's, by Clark Mazur,[1] when he introduced the first concept of GIST. The first mutation on the KIT oncogene was first documented in 1998, by Hirota.[2] Until then, most GISTS' were classified as leiomyomas, leiomyosarcomas or leiomyoblastomas.

Epidemiology

GISTs were in time considered an indistinct tumor, but are now considered a distinct neoplasm entity, with a particular histology, immunehistochemistry, molecular and oncogenic profile. Its worldwide incidence is estimated of around 1/1 00 000/year, and 10 cases per million in Europe.[3] Prevalence rounds about 130 cases per million population.[3] GISTs are more common in people older than 50 years old (>80%), rare under 20 years old (0-4%), and have similar frequencies in both sexes.

Clinical Presentation

Most GISTs are asymptomatic when small. Signs and symptoms are normally related to the location and size of the tumor. A mild gastrointestinal pain or discomfort can appear in 50-70% of the cases, GI hemorrhage in 50% cases, palpable tumor mass and also constitutional symptoms such as, anorexia, weight loss, fatigue, dyspepsia, dysphagia, nausea or vomiting, constipation or diarrhea and abdominal pain. Acute intraperitoneal bleeding leading to anemia or bowel perforation may also occur. At presentation, 15-50% of GISTS are metastatic. These are commonly found inside the abdominal cavity, namely in the liver, peritoneum and omentum and other sites.

Pathology

GISTs have three distinct histological patterns such as spindle cell, epithelioid and mixed. Being these patterns common with other tumors affecting also the gastrointestinal tract, immunohistochemistry markers are used to confirm the diagnosis. The most sensitive and specific markers for GISTS are CD117 (KIT) and DOG1 (ANO1-anoctamin 1) which are positive in more than 95% of GISTs. Only about 5% of GISTs are negative for KIT expression, but many of these are positive for DOG1. They also stain for CD34 in 70% of the cases, SMA (smooth muscle actin) in 15-60% and also stain for protein S100 around 10%. GISTs rarely express desmin.[4]

Risk Stratification of GIST

The risk stratification of GISTs is determined by analyzing three factors: tumor size, mitotic index and tumor location. This permits to characterize the risk of recurrence after surgery, and classify them in different groups: very low risk patients, low, medium and high risk patients, according to the model of "NIH" (National Institutes of Health).[5] Patients with very low risk and low-risk tumors can perform only surgery; the intermediate risk and high risk may be indicated for adjuvant treatment. Emphasis on tumors where rupture of the tumor capsule occurs, always have indication for adjuvant treatment.

Oncogenic Pathway

In GIST, in 90% of cases occurring mutations in two oncogenes: the oncogene KIT (also known as CD117), where there are about 75-80% of the mutations, the most frequent of exon 11 and exon 9; *PDGFRA* oncogene (α receptor platelet-derived growth factor), where mutations occur in 10% of patients.

A sub-group of GIST's, 10-15%, lack mutations in the oncogene KIT and oncogene *PDGFRA*. These are called wild-type GISTs. They englobe a heterogeneous group, which includes NF1 mutation, Carney-Stratakis syndrome, Carney's

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-115

triad, BRAF mutations, succinate dehydrogenase subunit mutations (SDHA, SDHB, SDHC, SDHD) and RAS- family mutations too.

There may also be other changes, in particular in BRAF and NF1 (<2%) and SDH (succinate dehydrogenase) in approximately 10%. These subtypes of mutations have prognostic implications, including: point mutations in exon 11 of KIT oncogene (65%) which confers a favorable prognosis; mutations in exon 9 KIT oncogene (9%) are associated with poor prognosis; *PDGFRA* D842V mutations are associated with good prognosis in initial tumors, but the poor prognosis in metastatic GITS.

Treatment

According to an analysis of a pooled population-based cohorts, which included 2459 patients, estimated 5-year survival and 15 year recurrence-free survival rates for GIST treated with surgery alone was respectively 70.5% and 59.9% respectively.[6] Since then, surgery has been considered the state of art for localized GISTs, as most patients with operable GISTs are probably cured. GISTs have been considered chemoresistance as has been demonstrated in several studies, were the response rate was less than 5% with a median survival for advanced disease was approximately 18 months.[4] On the other hand, few data suggests that GISTs are sensitive to radiotherapy. It may have indication in a palliative situation, such as relief of symptoms, with a cumulative target dose of 30-50 Gy delivered in 2-3 Gy daily fractions.[7] In the early 1990's, Imatinib is a tyrosine inhibitor, was developed as a treatment for chronic myelogenous leukemia due to its capacity of inhibiting the fusion oncoprotein BCR-ABL. Due to structural similarities with KIT, several other experiments showed that imatinib can also inhibit the growth of cells that express mutant forms of KIT.[8] Imatinib has been recommended for GIST tumors with KIT imatinib-sensitive mutations.

Early GIST

The drug of choice for treatment in the adjuvant setting has been Imatinib where positive results have been demonstrated in two randomized trials. An American trial, ACOSOG Z9001,[9] 713 patients were randomized into two arms (imatinib *versus* placebo); a statistically significant impact on recurrence-free survival in the imatinib group was demonstrated. In the European study AIO,[10] 400 patients with operable GIST were randomized with a high risk of recurrence in two groups: one received imatinib for 12 months and the other imatinib for 36 months. After five years, the results showed to be more favorable in the arm of patients treated for 36 months, concerning recurrence-free survival and overall survival.

Advanced GIST

In cases where a patient was treated with imatinib and developed metastases to the liver, one of the recommendations may be increasing the dose according to the patient's tolerance and their comorbidities, where a good partial response or a stable disease may be accomplished.[11]

Sunitinib, is a second-line therapy, tyrosine kinase inhibitor, which is active in cells with mutations in exon 11 KIT and secondary exon 13 mutations (V654A) and exon 14 (T6701) of KIT, which confer resistance to imatinib, and, in fact, that demonstrated by a free time increase to progression (6.3 *versus* 1.5 months), a randomized trial of sunitinib *versus* placebo.[12]

Progression after imatinib and sunitinib can develop new mutations that confer resistance to these treatments. In this situation there are few alternatives. The use imatinib after a first approach with imatinib or sunitinib, in the study RIGHT (Rechallange of Imatinib in GIST Having the effective Treatment) did not lead to benefit in OS, but conducted to an increase in median PFS.[13]

For third-line treatments a new molecule appeared regorafenib, an oral, multikinase inhibitor which acts against *KIT*, *PDGFR* and *VEGFR*. It inhibits the tumor micro-environment (*PDGFR, FGRF*), proliferation of certain tumor cells (*KIT, RET, RAF-1, BRAF, BRAF V600E*) and also neo angiogenesis (*VEGFR 1, 2, 3, TIE2*). In the GRID study[14] (Regorafenib in Progressive Disease phase III study design), 199 patients previously treated with imatinib and sunitinib, with metastatic unresectable GIST, were randomized (2:1) into two groups: one group of patients treated with regorafenib ID 160 mg every 21 days and best supportive care *versus* another group treated with placebo and best supportive care. There was a statistically significant increase in PFS (primary end point of the study), 4.8 months *versus* 0.9 months, with clear superiority of regorafenib arm, with a 73% reduction in the risk of progression or death. It was not demonstrated benefit of OS, but there was "crossed-over" between the arms, the patient progressed on placebo were, many of them subsequently included in the regorafenib arm. The most common side effects were related regorafenib hand-foot syndrome, hypertension, and diarrhea. After this test, in August 2014, regorafenib is approved for use in metastatic GIST after failure of treatment with imatinib and sunitinib.

AIM

To evaluate fifteen years of experience in managing GISTs on a peripheral Portuguese Hospital. Define the behavior of GIST's and the association between the histological, immunohistochemistry characteristics and disease progression. Question if the optimal treatment was delivered in GIST patients, based on medical evidence, where limitations on evaluating molecular signatures exists.

MATERIAL AND METHODS

Ethical Considerations

The study was reviewed and approved by the Oncology Depart-

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ment of Centro Hospitalar entre Douro e Vouga, Institutional Review Board.

Data Analysis

A retrospective analysis of cases treated in Hospital of Entre Douro and Vouga from 1 January 1999 to 31 December 2014. Demographic characteristics were evaluated variables related to tumor and disease progression. All patients were evaluated in a multidisciplinary team. An expert treatment decision was made according to the National Institute of Health criteria of Gastrointestinal stromal tumor's risk of recurrence after surgery.

Statistical Analysis

Statistical study was performed using SPSS version 21.

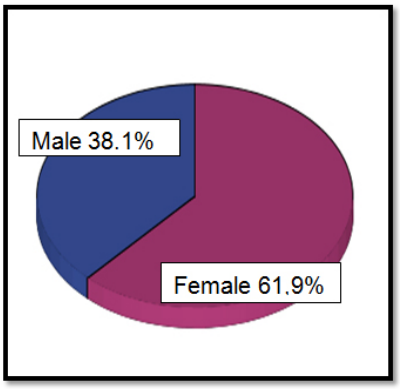
RESULTS

There have been 63 cases, 61.9% in female patients and 38.1% male (Graphic 1). The median age at diagnosis was 69 years (Graphic 2). As can be observed in (Graphic 3), a progressive increase in the incidence of GISTs was documented since 1999 to 2014. The most common source locations were: stomach (71.4%), small bowel (17.5%) and appendix (7.9%) (Graphic 4). When assessing the Mitotic count (Graphic 5), 27% was superior to 5mitosis/50HPF and 73% was inferior to 5mitosis /50HPF. In total, 62 patients underwent surgery with R0 resection rate of 94%. No tumor rupture occurred either before or after surgery. R1 resection occurred in 4.8% (n=3) of the patients. One patient wasn't submitted to surgery. Immunohistochemistry was performed in all patients, and sixty-one patients were positive for CD117. Only two patients were CD117 negative. No KIT gene mutation analysis was performed.

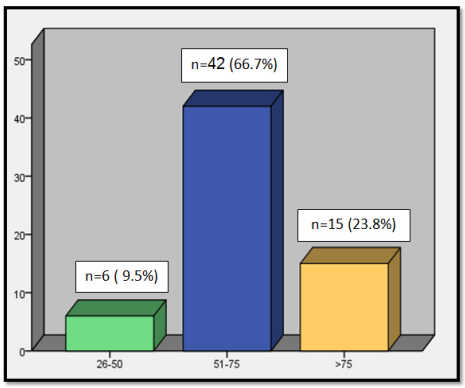
Regarding the biological risk of recurrence or metastasis, according to the National Institute of Health (NIH), 25,4 % of the patients had a very high risk, 19,0% had an intermediate risk, 34,9% had a low risk and 20,6 % had a very low risk (Graphic 6).

Of the 63 patients, 25.4% (n=16) were submitted to adjuvant treatment with imatinib (400 mg/daily) during 3 years (Graphic 7). Form this analysis 71.4% had tumors of very high risk, while only 12.2% had low risk.

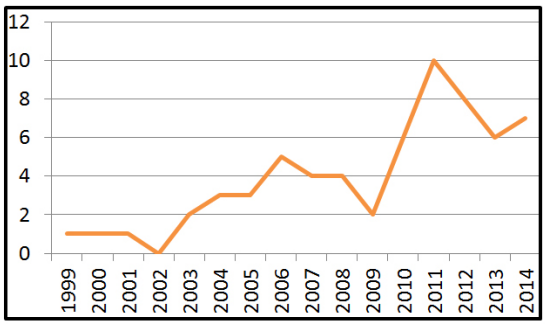
Only 7.9% (n=5) received palliative treatment with imatinib and sunitinib (Graphic 8). When analyzed, 3 patients were submitted to metastesectomy after progression, with an overall survival from a minimum of 4 to a maximum of 11 years



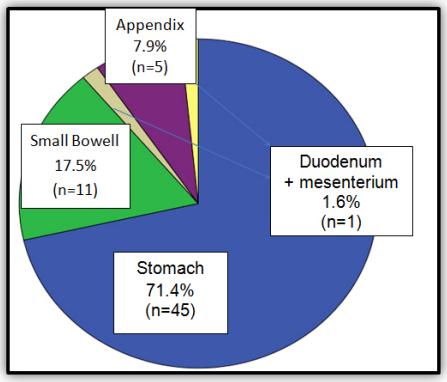
Graphic 1: Distribution by sex (n=63).



Graphic 2: Distribution by age.



Graphic 3: Incidence of GISTs during 15 years of experience.



Graphic 4: Tumor localization.

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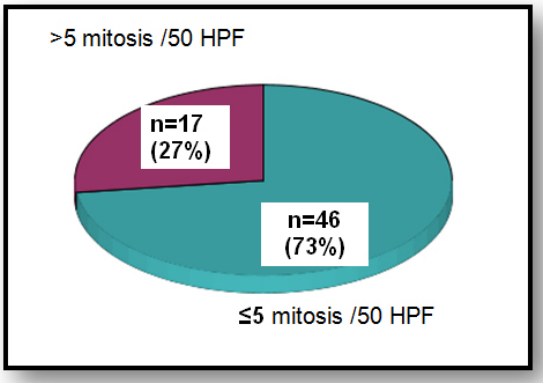
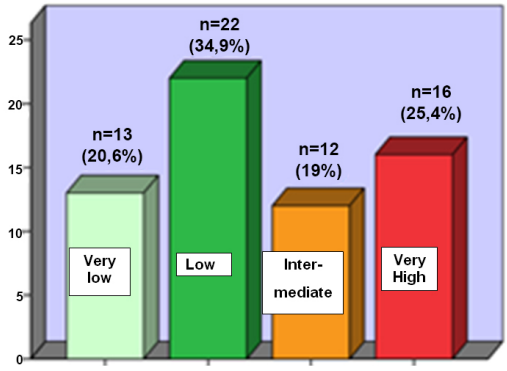
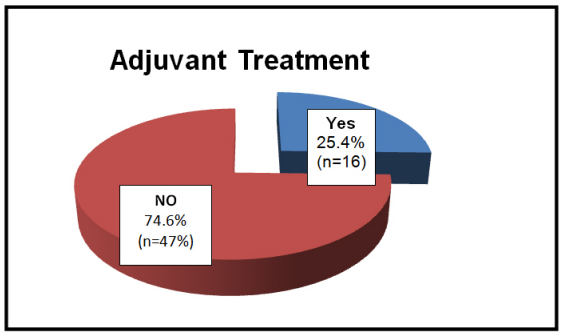


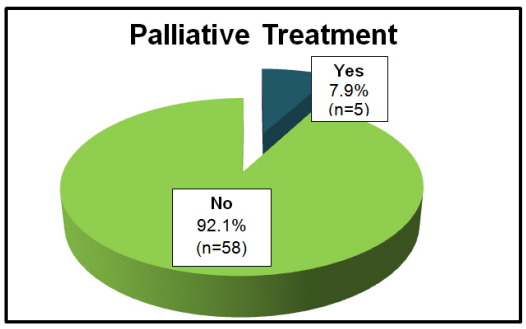
Graphic 5: Mitotic count.



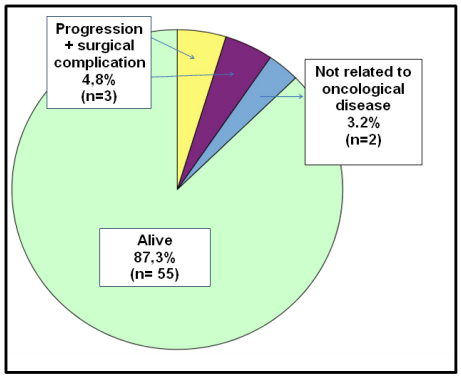
Graphic 6: Distribution of GISTs by the NIH classification.



Graphic 7: Patients under Adjuvant Treatment.



Graphic 8: Patients under Palliative Treatment.



Graphic 9: Results.

until the last evaluation.

Two of the patients submitted to palliative treatment are alive, having survived from a minimum of four years to a maximum of 14 years. Three patients died after disease progression. In 11% of patients the disease progressed (median time to progression of 36 months). The mortality rate was 12.7% (n=8) and only three died of progressive disease. However, 55 patients were alive (87.3%) at the end of this retrospective study (Graphic 9).

DISCUSSION

Strengths and Weaknesses of the Study

The mutation analysis is critical in the clinical decision on adjunctive therapy, as with the cases of the KIT exon 9 mutation may respond favorably to the increase in dose of imatinib, while the genotypes PDGFRA D842V mutations are less sensitive or resistant to imatinib.

In our Hospital the above-mentioned mutations were not studied, which might have influenced the treatment and prognosis of our patients. Nevertheless, an increase of diagnosis of GIST was observed since 1999, as physicians became more aware of this new entity. The survival rate of patients studied was high (87%). This may be justified by the fact that most of the patients were very low or low risk (55.5%) and also to the fact that in 94% of the cases, R0 resection was accomplished. It was found that only patients who had high biological disease risk, showed progression and mortality associated with cancer disease.

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-115

FUTURE SRATAGIES

Based on pharmaco-economic studies recently published in Oncologist[15,16] it has been emphasized that adjuvant treatment with imatinib must not be neglected, based on mutational analysis and dose administration. This is justified by a significant economic impact on the national health system, and on the other hand, its adequate use concerning dosage and mutational status, allows a better approach to cost-benefit level for each patient.

On a palliative point of view, GISTs' recurrence is also associated with an economic and social cost that must be brought up.[17] The optimization of the therapeutic target in the treatment of GISTs will provide an overall benefit concerning the patient and its physician, with a tailored molecular therapy and life-saving approach. More pharmoco-economic studies focusing the importance of further molecular characterization of this disease must be supported and carried out, not only for care-saving but also for health-saving of the national health system.

ACKNOWLEDGEMENTS

The authors thank to the participating team involved in elaborating this study directly and indirectly.

AUTHORS CONTRIBUTION

Joana Espiga de Macedo and Pedro Santos contributed to study conception, design and writing article; editing and reviewing; Sílvia Lopes and Mónica Pinho contributed to date acquisition, data analysis and interpretation; Joana Espiga de Macedo contributed for the final approval of the article.

SUPPORTED FOUNDATIONS

Joana Espiga de Macedo and the Department of Medical Oncology, Centro Hospitalar de Entre o Douro e Vouga, Portugal.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was reviewed and approved by the Department of Medical Oncology, Centro Hospitalar de Entre o Douro e Vouga, Institutional Review Board.

INFORMED CONSENT

All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

CONFLICTS OF INTEREST

Joana Espiga de Macedo has received fees for serving as a speaker, such as consultant and/or an advisory board member for Celgene, Merck and Roche. Silvia Lopes, Mónica Pinho and Pedro Santos have no conflict-of-interest.

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CANCER STUDIES AND MOLECULAR MEDICINE

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ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-116

Research

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Volume 3 : Issue 1
Article Ref. #: 1000CSMMOJ3116

Article History
Received: September 12th, 2016
Accepted: October 18th, 2016
Published: October 19th, 2016

Citation
Al-Olah Y, Al-Qhtani NM, Al Waheeby MMA, et al. Rounding down chemotherapeutic agents to the nearest vial size as a cost containment measure. *Cancer Stud Mol Med Open J*. 2016; 3(1): 14-18. doi: 10.17140/CSMMOJ-3-116

Rounding Down Chemotherapeutic Agents to the Nearest Vial Size as a Cost Containment Measure

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ABSTRACT

Background: High cancer treatment costs significantly affect health care expenditures. Drug waste reduction of costly drugs can reduce the treatment cost.
Methods: A retrospective study conducted at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia. Adult patients above age of 14 years old who received chemotherapy between March 1st to March 31st, 2015 were included. Maximum dose rounding allowed was up to 10% for palliative intent and 5% for curative intent. Patients demographics, diagnosis, treatment intent (cure or palliation), ordered dose, rounded dose, vial size, number of vials that could be saved and expected cost saved per month were calculated and recorded.
Results: A total of 305 patients received 973 doses of intravenous chemotherapy drugs during the study period. Orders of 352 doses could be rounded to the nearest vial size with a 10% dose deviation for palliative intent and 5% for curative intent. The projected savings for 1 month was calculated to be Saudi Riyals (SR) 14,720.95 for 5% rounding limit and SR 53,157.50 for 10% rounding which will account to an estimate of SR 814,514.40 of drug cost savings per year. Anti-cancer drugs with the most drug wastage due to non-rounding to the nearest vial size were trastuzumab, cyclophosphamide, etoposide, methotrexate, fluorouracil, paclitaxel, oxaliplatin, doxorubicin, bortezomib, and cytarabine consecutively. The highest costs savings when rounding the doses to the nearest vial size up to 5% for curative intent was associated with rituximab, followed by fludarabine and paclitaxel. Bevacizumab, cetuximab, and carfilzomib have resulted in the most cost savings when the rounding limit was set to 10% for palliative intent.
Conclusion: Dose rounding of the ordered dose to an amount within 5% for curative intent and 10% for palliative intent to the nearest vial size has resulted in a valuable cost savings through reduction of drug wastage without any expected compromise in efficacy.

KEYWORDS: Chemotherapy wastage; Dose rounding; Cost-saving.

ABBREVIATIONS: AHRQ: Agency for Healthcare Research and Quality; BSA: Body Surface Area; FDA: Food and Drug Administration.

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-116

INTRODUCTION

The strong upward rise in cancer-drug prices and spending has provoked concern on drug wastage and called for a search of saving measures. Cancer is one of the top leading causes of death worldwide and considered as the 2nd most common cause of death in the United States. About 589,430 American are expected to die of cancer in 2015, that's about 1,620 people per day. The expected number of newly diagnosed cases of cancer in American population in the year of 2015 is around 1,658,370 cases. The Agency for Healthcare Research and Quality (AHRQ) estimated that the direct medical costs for cancer in the US in 2011 was $88.7 billion.[1] In 1990, costs of cancer care were estimated to be 27 billion dollars, rising to 90 billion dollars in 2008, and expected to be around 157 billion dollars by 2020, which is almost a 600% increase over the past 3 decades.[2,3]

With the rising costs of cancer care and number of newly introduced expensive therapies, cost containment strategies are important. Drug wastage as a consequence of unused or partially used vials can be costly, while dose rounding of both chemotherapeutic and biologic anti-cancer agents to the nearest vial size has resulted in substantial cost savings.[4] It entails calculating the dose of drug based on the patient's body surface area (BSA) and the approved dosing regimen. The calculated dose is then rounded within a percentage limit (10% is the most commonly used in the literature) to the nearest vial size. This approach have been found to reduce drug wastage and to be more cost effective, since it permits the complete use of the content of any given vial.[5]

In this study, we investigated the potential cost savings associated with dose rounding of standard chemotherapy regimens to the nearest vial size.

METHOD

This retrospective quantitative study was conducted at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia oncology satellite pharmacy. Preliminary data were collected from chemotherapy pharmacy satellite work sheet for the period of the study starting March 1st to March 31st, 2015. All adult patients aging 14 years and older with a diagnosis of cancer for which they have received anti-cancer agents during the study period were included (N=305). Doses of anti-cancer drugs were calculated based upon the patient's BSA and the Food and Drug Administration (FDA) approved recommended dosing regimen. The exact total dose was then theoretically rounded to the nearest vial size. The maximum dose rounding allowed was 10% for palliative intent treatment and 5% for curative intent treatment. The rest of the demographic data were completed from the computerized health information system (Quadra-Med) using a data collection sheet. The new theoretically rounded doses costs were analyzed to estimate the potential cost savings in comparison to the actually dispensed doses considering the maximum allowed rounding to the nearest vial size (5% for curative intent and 10% for palliative intent). The potential effect on cost was calculated in Saudi Riyals (SR) for both the actual doses dispensed calculated and rounded doses. Drug wastage was defined and calculated as the amount of drug (number and size of vials) that may have been saved if the rounding to nearest vial size was implemented. Data collected included drug name, ordered dose, rounded dose, number of product vials wasted, and drug direct cost. In our study, all Institutional Review Board (IRB) procedures were followed.

RESULTS

A total of 305 patients received 973 doses of intravenous chemotherapy and anti-cancer biological agents during March 2015. Among these 973 doses, 352 doses could be rounded to the nearest vial size with a 10% dose deviation for palliative intent and 5% for curative intent. The projected savings for one month was calculated to be SR 14,720.95 for 5% rounding limit and SR 53,157.50 for 10% rounding which accounts to an estimate of SR 814,514.40 of drug wastages per year (Table 1). Anti-cancer drugs with the most drug wastage were trastuzumab, cyclophosphamide, etoposide, methotrexate, fluorouracil, paclitaxel, oxaliplatin, doxorubicin, bortezomib, and cytarabine consecutively (Figure 1). The highest costs savings when rounding the doses to the nearest vial size up to 5% for curative intent were asso-

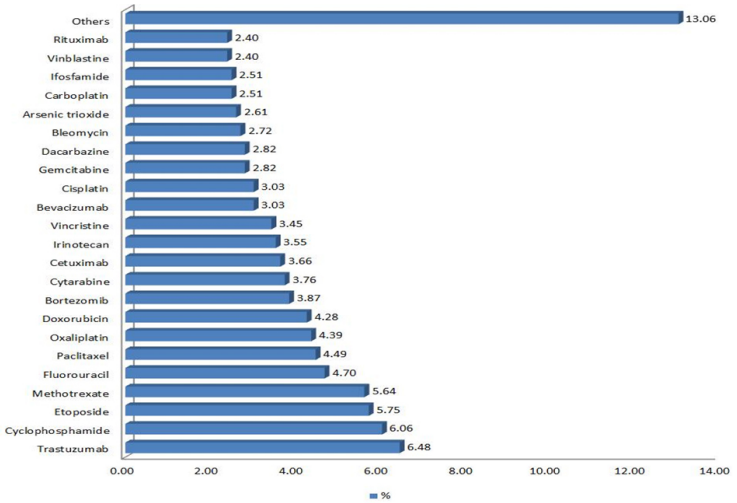

Figure 1: Anti-cancer agents with the most drug wastages saved when rounding to the nearest vial size.

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-116

Intent of treatment (Cure of Pallation)	Medication	Sum of # of Vials saved 2	Sum of cost saved (1 mo) SR.	Sum of cost saved (12 mo) SR.
Cure (Rounding up to 5%)	Cisplatin	3	85.05	1,020.60
	Cyclophosphamide	14	653.80	7,845.60
	Cytarabine	2	299.20	3,590.40
	Etoposide	2	586.20	7,034.40
	Fludarabine	3	4,889.25	58,671.00
	Methotrexate	1	21.65	259.80
	Paclitaxel	4	2,309.60	27,715.20
	Rituximab	2	5,876.20	70,514.40
Toatal		**31**	**14,720.95**	**176,651.40**
Pallation (Rounding up to 10%)	Bevacizumab	10	15,505.00	186,060.00
	Carboplatin	3	583.50	7,002.00
	Carfilzomib	1	8,250.00	99,000.00
	Cetuximab	9	11,844.00	142,128.00
	Cisplatin	2	85.05	1,020.60
	Cyclophosphamide	8	373.60	4,483.20
	Cytarabine	3	448.80	5,385.60
	Docetaxel	2	1,430.00	17,160.00
	Fluorouracil	2	50.50	606.00
	Gemcitabine	14	1,757.00	21,084.00
	Irinotecan	4	2,086.80	25,041.60
	Oxaliplatin	12	2,962.20	35,546.40
	Paclitaxel	8	4,619.20	55,430.40
	Rituximab	1	2,938.10	35,257.20
	Vinblastine	1	223.75	2,685.00
Toatal		**80**	**53,157.50**	**637,890.00**
Grand Toatal			**67,878.45 (18,101 USD)**	**814,541.40 (217,211 USD)**

Table 1: Cost saving from rounding up to 5% for curative intent, and up to 10% for palliation intent.

ciated with rituximab, followed by fludarabine and paclitaxel. Bevacizumab, cetuximab, and carfilzomib have resulted in the most cost savings when the rounding limit was set to 10% for palliative intent. In our study we found out that around 38.69% (N=118) of the patients were treated with a curative intent while 61.31% (N=187) of the patients received palliative chemotherapy (Figure 2). The most common type of cancer was breast cancer which has been seen in about 20% (N=61) of the cases (Figure 3). Female patients comprised 59.67% (N=182) of the patients and those who aged between 51-60 years were the most age group to receive chemotherapy agents 21.64% (N=66) (Figures 4 and 5).

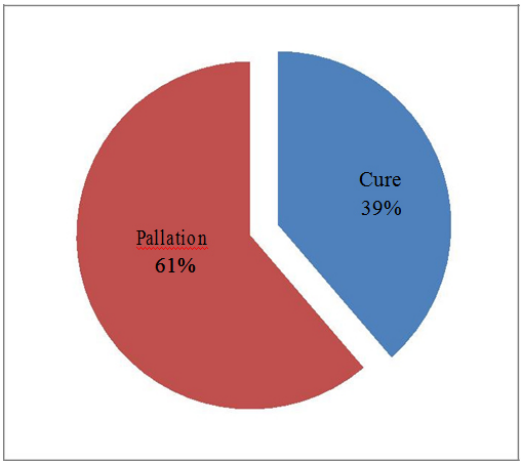

Figure 2: Treatment intent.

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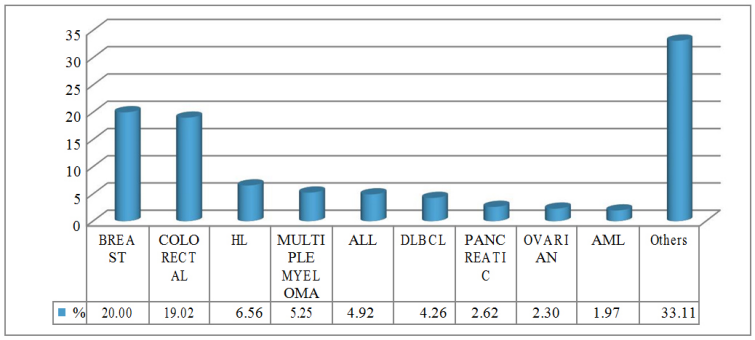

Figure 3: Diagnosis.

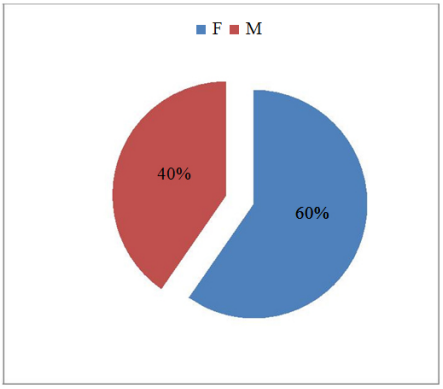

Figure 4: Gender.

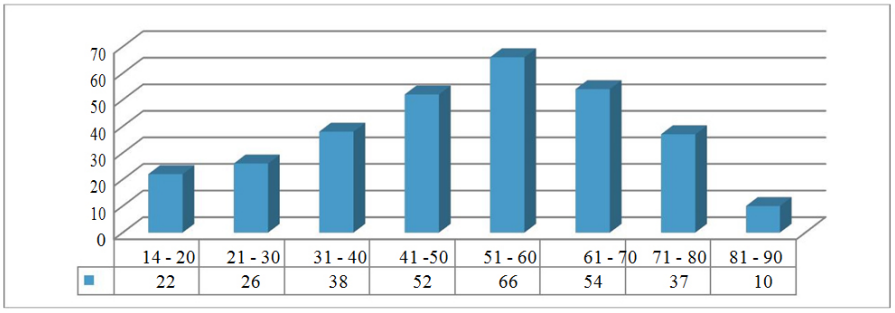

Figure 5: Age group.

DISCUSSION

A significant and progressive cost rising in medical oncology due to the incorporation of novel and highly expensive drugs into clinical practice have been seen in the past years. Intravenous cancer agents are typically supplied in fixed drug amount vials, allowing the use of partial vials for a given patient. Some drugs, and the majority of monoclonal antibodies, are packaged preservative free, allowing only for single time uses with a short expiration. When expensive new drugs, such as monoclonal antibodies or other biologics, are made preservative-free and used infrequently, unused partial vials that have expired can account to a large amount of drug wastage. Drug wastage is defined as the consequence of an inappropriate disposal of unused or partially used drug vials or syringes.[6] Dose rounding is an option which might be used in oncology settings to cut down extra costs due to drug wastages. Literature suggests that dose rounding of chemotherapy and biologic drugs to an amount of up to 10% of the ordered dose is a significant cost-containment in an era of rising health care costs without adverse effects or a negative impact on the treatment outcomes.[5]

For instance, rituximab which is available as 400 mg and 100 mg vials, if the calculated dose is 720 mg, it could be rounded to 700 mg by 2.8% dose deviation. In such a case, one 100 mg vial will be saved and limit a potential distinct economic loss. Brenda et al[5] found that dose rounding could reduce drug wastage for up to 42% and resulted in a potential cost savings of $24,434 for 3-month interval. In another study done by Nagwa Ibrahim, [7] dose rounding of anti-cancer agents may save around $192,800 per year. Our study reveals that the projected annual saving was calculated to be SR 176,651.40 for 5% rounding limit and SR 637,890.00 for 10% rounding which will account to an estimate of SR 814,514.40 ($217,204) of drug wastage per year. Trastuzumab, and cyclophosphamide were the most anti-cancers associated with drug wastage. Rituximab has resulted in

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-116

the highest costs of drug wastage when rounding the doses to the nearest vial size up to 5 % for curative intent. While bevacizumab, and cetuximab have resulted in the most cost savings when rounding to 10% for palliative treatment. Female patients were more to receive chemotherapy than males in our population and this could be correlated with the fact that the most common type of cancer in our study to receive chemotherapy was breast cancer. Around 61.31% of chemotherapy orders were for palliative intent treatment which could allow more space for rounding up to the limit of 10% to the nearest vial size and contribute to more potential cost savings. The most age group to receive chemotherapy in our study was those who aged 51-60 years 21.64% (N=66) followed by those who aged between 61-70 years old 17.70 % (N=54).

In our study, dose rounding of anticancer agents to an amount within 10% of the ordered dose has resulted in cost savings through reduction of drug wastage in our institution and is consistent with the findings of other studies. As it is a one month retrospective study, a prospective study with a longer duration and a larger population might help in getting a more accurate projection of drug wastage and cost savings with dose rounding strategy to the nearest vial size. Clinical outcomes of dose rounding could be another future research focus as well. Dose-rounding interventions by a pharmacist are feasible and an automatic dose-rounding protocol is desired to assist in reining the rising cancer drugs expenditure.

CONCLUSION

Dose rounding of the ordered dose to an amount within 5% for curative intent and 10% for palliative intent to the nearest vial size has resulted in a valuable cost savings through reduction of drug wastage.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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