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Biomarkers in breast cancer: Quantifying discordance with best practice when hormone receptor status is an extravagance

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Background: In Zimbabwe, the hormone receptor status is not always available when patients with breast cancer are started on treatment.

Aim: This study evaluated the discordance of treatment approach in such patients, with National Comprehensive Cancer Network (NCCN) guideline recommendations as the reference standard when these results are eventually available.

Setting: Female patients who presented to the Parirenyatwa Central Hospital Radiotherapy and Oncology Centre with a histological diagnosis of breast cancer, managed between 1 January 2014 and 31 December 2016.

Methods: Patients with breast cancer having unknown receptor status at diagnosis, and the hormone receptor status were subsequently available either clinically or the tissues were available for study-specific analysis, were eligible for the study. The level of agreement between treatments received and the NCCN recommendations if the receptor status was known was tested using Kappa statistic.

Results: Patients in stage I–III received treatment that were in strong agreement with the use of chemotherapy, and endocrine treatments with agreement scores of 1 (95% CI 0.91–1) and 0.81 (95% CI 0.65–0.95), respectively; but moderate agreement with regard to the choice of chemotherapy regimen, with a score of 0.5 (95% CI 0.32–0.68). There was a median delay of 8 (range 3–27) months for the availability of receptor status. Of the 38 stage IV patients, 33 (87%) were recommended chemotherapy. Of the 38 patients, 25 (66%) had hormone driven disease. There was somewhat agreement for use of chemotherapy, choice of chemotherapy regimen and use of endocrine treatments as initial choice with agreement scores of 0.53 (95% CI 0.36,0.69), 0.18 (95% CI 0.07, 0.35) and 0.68 (95% CI 0.51,0.82) respectively.

Conclusion: Treatment approaches were largely in agreement with the NCCN guidelines for patients in stage I–III. Discordance was noted in stage IV patients with under-utilisation of hormone therapy as the initial treatment when the receptor status was unknown.

Keywords: breast cancer; biomarkers; treatment guidelines; limited resources; sub-Saharan Africa.

Background

Great strides have been made worldwide in the treatment of breast cancer, with improved outcomes in the last three decades notably in developed countries.[1] This is attributed to the new therapeutic approaches that are biomarker based and supported by several clinical trials. Traditionally, therapeutic options were largely based on stage, grade and histology amongst other prognostic factors. As technical tools were developed, biomarkers in DNA, RNA and protein levels provided an in-depth knowledge in understanding the biology of the tumour.[2]

More than 50% of breast cancer cases in sub-Saharan African countries present with local advancement to metastatic disease.[3] Management protocols are stratified according to luminal subtypes, with 70% of primary breast cancer being hormone driven.[4] Favourable toxicity profiles make hormone therapies an attractive option. Clinical trials have shown a survival advantage for women with hormone-receptor-positive tumours treated with adjuvant hormone and/or certain chemotherapeutic regimens.

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Results from clinical trials consistently support the benefit of endocrine therapy both in premenopausal and in postmenopausal women when indicated.[5]

Overexpression of human epidermal growth factor receptor is found in 20% of primary breast cancer and entails a worse prognosis. However, its presence predicts good response to treatment with anti-human epidermal growth factor receptor 2 (HER2).[6] Trials on HER2/neu-positive breast cancer show the benefit of trastuzumab in overall and progression-free survivals.[7] As a result, the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and St Gallen have developed guidelines centred on the evolution of molecular profiling. A limitation, however, is that in many countries biomarkers are not readily available at all institutions managing breast cancer. In Zimbabwe, an additional US$150 is required for three common markers' immunohistochemistry (ER, PR and HER2 neu), which is more than the cost of initial histology. This cost must be borne out of pocket by all patients, including those with medical insurance because it has not yet been incorporated into the medical insurance tariffs along with the traditional H&E staining and reporting. This is a major prohibitive factor for the generalised adoption of biomarkers to support treatment decisions in resource-limited settings such as Zimbabwe, as recommended by the NCCN guidelines. The NCCN guidelines have recently embarked on an initiative to assist those physicians who work with limited resources as noted by the formulation of guidelines for basic, core and enhanced resource setting.

The objectives of our study are to describe the therapeutic approaches of patients with breast cancer having undefined hormone receptor profiles at the time of diagnosis, who were managed at a Zimbabwean institution, and to ascertain the level of concordance with NCCN guideline recommendations as the reference standard.

Methods

A retrospective analysis of female patients who presented to the Parirenyatwa Central Hospital Radiotherapy and Oncology Centre (The Unit) with a histological diagnosis of breast cancer, managed between 01 January 2014 and 31 December 2016, was undertaken. Patients seen in the public sector who had initial treatment recommendations with no knowledge of the tumour receptor status were identified. Hormone receptor status of this cohort was retrospectively acquired for the purpose of this study. Patients were excluded if they defaulted from completing the clinical assessments before treatment recommendations were made, if there were missing records on management options or if the initial pathology was not processed at our laboratory precluding evaluation of their hormone status. A study-specific data abstraction form was used to extract data from hospital files on relevant study variables, which included patient and disease characteristics, therapeutic options of chemotherapy, endocrine therapy, targeted therapy, radiotherapy and best supportive care. Menopausal status was as recorded from files. If undocumented, age greater than 60 was regarded as postmenopausal based on the NCCN definition by age. The time to receptor status availability from initial pathology was recorded up to the time of data collection, that is, December 2017. Chemotherapy recommended according to the NCCN guidelines for stage I–III was Adriamycin, cyclophosphamide and taxane (ACT) and for stage IV, when applicable, single-agent chemotherapy was administered.

Statistical analysis

Categorical variables were described using frequencies and percentages, and continuous variables are summarised using median and range. Fisher's exact test was used to assess the relationship between intrinsic subtypes and categorical variables (HIV status, menopausal status, performance status, age group, family history and gender). A p value of < 0.05 was considered statistically significant. Therapeutic approach recommendations between the unit (without hormone receptor status) and the NCCN guidelines (if hormone receptor status was known) were presented in a contingency table. The overall proportion of agreement between the two was estimated by the number of cases where both agree divided by the total number of cases considered, with 95% exact Clopper–Pearson confidence interval (see Table 1 for scaling). R version 3.5.2 (R Core Team (2018) was used for statistical analysis. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (URL https://www.R-project.org/.)

Ethical consideration

Ethical clearance and permission to carry out the study was obtained from Joint Research Ethics Committee for the University of Zimbabwe, College of Health Sciences and Parirenyatwa Group of Hospitals (JREC REF: 347/17) prior to initiation of the study. Ethical Clearance was received on 27 November 2017.

Results

During the 3-year period, a total of 426 patients presented with histology-confirmed breast cancer at the unit. Of these, 295 patients with complete records were identified, of which 197 (67%) patients did not have results for hormone receptor status at the initial presentation before management was instituted. Ultimately, only 80 patients had receptor status eventually retrieved and were eligible for the final analysis (see Figure 1 for patient exclusions).

TABLE 1: Scaling for the agreement – Kappa value interpretation (Landis and Koch (1977).[21]

Result and Description respectively	
< 0	No agreement between therapeutic approach at the unit and recommended by the NCCN based on biomarker
0.01–0.20	None to slight agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–1.00	Perfect agreement

Source: Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159–174

NCCN, National Comprehensive Cancer Network.

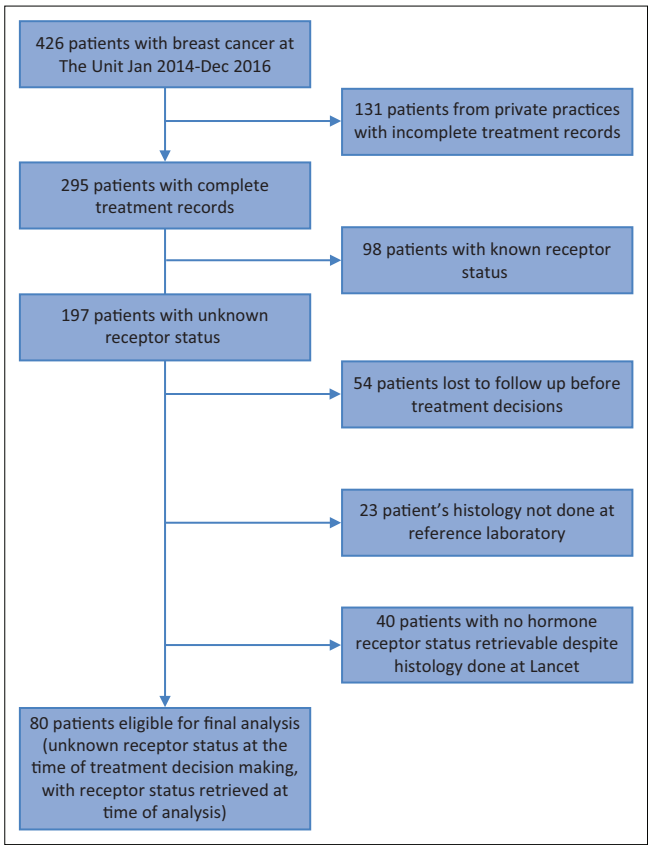

FIGURE 1: Flowchart of patient eligibility and reasons for exclusion.

Patient and disease characteristics

The median age was 52 years (range 15–85 years). Ten percent of patients was HIV positive but 20% had no documentation of HIV status, and 29 (36%) patients were premenopausal. The majority of patients, 56 (70%) of 80, had a good Karnofsky performance status of ≥ 80%. The most frequent intrinsic subtype was luminal A (50 patients; 62.5%) followed by triple negative (18 patients; 22.5%). Luminal B and HER2 enriched had six (7.5%) patients each. The common histology across all subtypes was ductal of intermediate grade. Stage IV disease (38 of 80; 47.5% of patients) was the most common stage at presentation. Of these, the majority had visceral metastasis (35 of 38; 92%) and the majority were luminal A (23 of 38; 60.5%). Lung metastases (20 of 38; 52.6%) were the most common followed by liver metastasis (9 of 38; 23.7%). Three patients (7.9%) had only bone metastasis and all were luminal A. Five patients were of undetermined stage as no staging investigations had been performed. Table 2 gives an overview of patient and disease characteristics.

Health insurance

Health insurance was not available for most patients, that is, 72 (90%) of 80. Eight patients had health insurance, but the hormone receptor status was not covered by their schemes, and they had to pay from their pocket.

Time to receptor status availability

The receptor status results of 80 patients were available at variable times after initial treatment decisions. Thirty-three patients' results were acquired at the time of data collection and 47 had results at variable times during treatments. The median time to receptor acquisition of the 47 patients was 8 (range 3–27) months post diagnosis.

Thirty-seven patients were eligible for hormone therapy as they were either estrogen receptor (ER) or progesterone receptor (PR) positive and were initiated on hormone therapy upon receipt of results. Only 3 of 14 patients received hormone treatment at the appropriate time according to treatment scheduling.

Therapeutic approaches for study patients, January 2014–2016

Surgery, systemic chemotherapy, radiotherapy, hormone therapy and best supportive care were the modes of therapeutic approaches recommended for definitive treatment. When indicated, multimodal treatment was instituted.

Concordance of therapeutic approaches in stage I–III patients

Chemotherapy

Chemotherapy was recommended as part of definitive management in 72 (90%) of 80 patients of which 37 patients had stage I–III breast cancer. All patients with stage I–III disease across all subtypes were recommended to receive either neoadjuvant or adjuvant chemotherapy. The common regimens prescribed as adjuvant or neoadjuvant therapy were cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) for 16 patients or doxorubicin, cyclophosphamide and paclitaxel (ACT) for 17 patients. Two patients had chemotherapy regimens other than the two common ones mentioned above and two were lost to follow-up prior to the prescription of chemotherapy. Table 3 depicts agreement between systemic therapy recommendations at the unit and the NCCN guidelines. Regarding the use of chemotherapy, the agreement score was 1 (95% CI 0.91–1) for stage I–III patients. However, the agreement on regimen choice was modest with an agreement score of 0.5 (95% CI 0.32–0.68).

Endocrine treatment

Of 37 the stage I–III patients, 29 (78%) had hormone-driven breast cancer. Of the 29 patients, 24 (83%) received endocrine treatment at variable times based on when the results for receptor status were available, with 22 of 24 receiving tamoxifen. The five who did not receive endocrine treatment had their results retrieved at the time of study. Overall, there was substantial agreement on hormone treatment between the NCCN guidelines and the unit for stage I–III patients with an agreement ratio of 0.81 (95% CI 0.65–0.92).

Concordance of therapeutic approaches in stage IV patients

Chemotherapy

Thirty-eight patients had stage IV disease, of which 33 were recommended to receive chemotherapy at initial presentation

TABLE 2: Patient and disease characteristics ($N = 80$).

Covariate	Full sample		HER2 enriched		Luminal A		Luminal B		Triple negative		p‡
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Number of patients	80	-	6	-	50	-	6	-	18	-	-
Family history of breast cancer	-	-	-	-	-	-	-	-	-	-	0.120
No	58	72	3	50	39	78	6	100	10	56	-
Unknown	13	16	1	17	8	16	0	0	4	22	-
Yes	9	11	2	33	3	6	0	0	4	22	-
Age group in years†	-	-	-	-	-	-	-	-	-		0.300
15–35	9	11	1	17	4	8	2	33	2	11	-
36–59	47	59	3	50	28	56	4	67	12	67	-
60+	24	30	2	33	18	36	0	0	4	22	-
HIV status	-	-	-	-	-	-	-	-	-	-	0.470
Negative	56	70	3	50	37	74	4	67	12	67	-
Positive	8	10	0	0	4	8	1	17	3	17	-
Unknown	16	20	3	50	9	18	1	17	3	17	-
Menopausal status	-	-	-	-	-	-	-	-	-	-	0.063
Postmenopause	51	64	4	67	33	66	1	17	13	72	-
Premenopause	29	36	2	33	17	34	5	83	5	28	-
Karnofsky performance status (%)	-	-	-	-	-	-	-	-	-	-	**0.044**
100	7	9	0	0	4	8	2	33	1	6	-
80–90	49	61	2	33	30	60	4	67	13	72	-
60–70	11	14	0	0	9	18	0	0	2	11	-
40–50	3	4	2	33	0	0	0	0	1	6	-
Not documented	10	12	2	33	7	14	0	0	1	6	-
Histological subtype	-	-	-	-	-	-	-	-	-	-	0.730
Ductal	71	89	5	83	43	86	6	100	17	94	-
Ductal and lobular	1	1	0	0	1	2	0	0	0	0	-
Lobular	5	6	1	17	4	8	0	0	0	0	-
Mucinous	1	1	0	0	1	2	0	0	0	0	-
Papillary	1	1	0	0	1	2	0	0	0	0	-
Unknown	1	1	0	0	0	0	0	0	1	6	-
Histological grade	-	-	-	-	-	-	-	-	-	-	0.860
1	4	5	0	0	4	8	0	0	0	0	-
2	44	56	3	50	27	55	4	67	10	56	-
3	22	28	2	33	11	22	2	33	7	39	-
Unknown	9	11	1	17	7	14	0	0	1	6	-
Missing	**1**	**-**	**0**	**-**	**1**	**-**	**0**	**-**	**0**	**-**	**-**
Stage	-	-	-	-	-	-	-	-	-	-	0.430
1	1	1	0	0	1	2	0	0	0	0	-
2	7	9	0	0	7	14	0	0	0	0	-
3	29	36	1	17	17	34	4	67	7	39	-
4	38	48	5	83	23	46	2	33	8	44	-
Unknown	5	6	0	0	2	4	0	0	3	17	-
Health insurance	-	-	-	-	-	-	-	-	-	-	0.360
No	73	91	5	83	47	94	6	100	15	83	-
Yes	7	9	1	17	3	6	0	0	3	17	-
Receptor status available at the time of study	-	-	-	-	-	-	-	-	-	-	0.230
No	47	59	4	67	31	62	5	83	7	39	-
Yes	33	41	2	33	19	38	1	17	11	61	-
Site of metastasis ($n = 38$)	-	-	-	-	-	-	-	-	-	-	-
Visceral liver only	9	24	3	60	4	17	0	-	2	25	-
Bone only	3	8	0	-	3	13	0	-	0	-	-
Visceral – lung only	20	53	2	40	13	57	2	-	3	38	-
Multiple sites	5	13	0	-	3	13	0	-	2	25	-
Brain only	1	2	0	-	0	-	0	-	1	12	-

†, Median (range) = 52 (15–85) years.

‡, Fisher's exact test.

as shown in Table 4. The remaining five patients (all luminal A) were recommended for best supportive care because of poor performance status. Twenty-five (66%) patients had hormone-sensitive (luminal A and B) breast cancer of which visceral disease was present in 22 (88%) of 25 patients. Visceral crisis was not confirmed in any of the patients. Bone metastasis as the only metastatic site was seen in 3 of 25 patients, and they were of luminal A subtype. Of the 33

patients, 23 (70%) receiving chemotherapy for metastatic disease were prescribed three-drug combination chemotherapy, commonly CAF, single-agent chemotherapy in 6 (18%) patients and the remaining 4 (12%) were prescribed a two-drug combination. Stratified by breast cancer subtypes summarised in Table 5, a good agreement was observed for chemotherapy as the initial treatment choice for HER2 enriched, luminal B and triple negative. The agreement scores were 1 for all with 95% CI of 0.48–1; 0.61–1 and 0.63–1, respectively, and the agreement score for luminal A was 0.22 (95% CI 0.07–0.44). The agreement score for choice of chemotherapy regimen between the unit and the NCCN guidelines for patients with stage IV disease, stratified by subtypes, was 0.4 (95% CI 0.05–0.85) for HER2 enriched, 0.17 (95% CI 0.04–0.41) for luminal A, (95% CI 0–0.84) luminal B 0 and 0.12 (95% CI 0–0.53) triple negative disease.

TABLE 3: Agreement analysis stage I–III patients (n = 37).

The unit recommendation	NCCN guidance recommendation		Agreement (95% CI)
	No	Yes	
Chemotherapy (n = 37)	–	–	1 (0.91–1)
No	0	0	–
Yes	0	37	–
Chemotherapy regimen (n = 34†)	–	–	0.5 (0.32–0.68)
No	0	17	–
Yes	17	0	–
Hormone treatment received (n = 37)	–	–	0.81 (0.65–0.92)
No	7	6	–
Yes	1	23	–

†, Of the 37 patients who were recommended to receive chemotherapy at the unit, 34 were prescribed a regimen.
NCCN, National Comprehensive Cancer Network.

TABLE 4: Systemic therapy agreement analysis for stage IV patients (N = 38).

The unit recommendation	NCCN guidance recommendation		Agreement (95% CI)
	No	Yes	
Chemotherapy (n = 38)	–	–	0.53 (0.36–0.69)
No	5	0	
Yes	18	15	
Chemotherapy regimen (n = 33*)	–	–	0.18 (0.07–0.35)
No	0	0	
Yes	27	6	
Hormone treatment received (n = 38)	–	–	0.68 (0.51–0.82)
No	13	12	
Yes	0	13	

*Of the 38 patients who were recommended to receive chemotherapy at the unit, 33 were prescribed a regimen.
NCCN, National Comprehensive Cancer Network.

Endocrine treatment

None of the stage IV patients with hormone-driven subtypes (n = 25) had hormone receptor status results at presentation. None of these patients had endocrine therapy as the first line therapy as per the NCCN guidelines. Those who later received endocrine treatment at some point during the treatment course, an agreement ratio of 0.68 (95% 0.51–0.82) was realised.

Discussion

Breast cancer is the most common malignancy in women worldwide.[8] Treatment is multimodal and evolving. Current approaches are based on molecular biomarkers such as ER, PR and HER2 neu status, which may not be readily available in some resource-constrained environments. In our study, when the minimum set of these characteristics, specifically hormone receptor status, was not available, management decisions were typically based on other parameters, which included stage, grade, lymph node involvement and histological subtype. We found 67% (197 of 295) of public patients was treated without the benefit for hormone receptor status at initial presentation. Of these, 70% had hormone-driven cancer.

Our finding of 67% of public patients presenting without hormone receptor status at initial presentation was consistent with that observed in other sub-Saharan African countries.[9] Of our cohort of 80 patients where treatment recommendations were known and hormone receptor status retrievable, 62.5% were luminal A and 7.5% luminal B, making a total of 70% hormone-driven breast cancer, comparable to 80% in a previous global review.[9] The lack of hormone receptor status is largely attributable to depressed socio-economic status. In our study, 90% of the patients had no health insurance; therefore, financial constraint is a probable cause of the low number of patients with hormone receptor status, which costs US$150. Population-based studies by region to determine the prevalent subtypes of breast cancer can help

TABLE 5: Systemic therapy agreement analysis for stage IV stratified by receptor status (N = 38).

Unit recommendation	HER2 enriched (n = 5)			Luminal A (n = 23)			Luminal B (n = 2)			Triple Negative (n = 8)		
	NCCN recommendation ⇑		Agreement (95% CI)	NCCN recommendation ⇑		Agreement (95% CI)	NCCN recommendation ⇑		Agreement (95% CI)	NCCN recommendation ⇑		Agreement (95% CI)
Chemotherapy	No	Yes	1 (0.48–1)	No	Yes	0.22 (0.07–0.44)	No	Yes	1 (0.16–1)	No	Yes	1 (0.63–1)
No	0	0		5	0		0	0		0	0	
Yes	0	5		18	0		0	2		0	8	
Chemotherapy regimen	No	Yes	0.4 (0.05–0.85)	No	Yes	0.17 (0.04–0.41)	No	Yes	0 (0–0.84)	No	Yes	0.12 (0–0.53)
No	0	0		0	0		0	0		0	0	
Yes	3	2		15	3		2	0		7	1	
Hormone treatment received	No	Yes	1 (0.48–1)	No	Yes	0.48 (0.27–0.69)	No	Yes	1 (0.16–1)	No	Yes	1 (0.63–1)
No	5	0		0	12		0	0		8	0	
Yes	0	0		0	11		0	2		0	0	

⇑NCCN Recommendation for chemotherapy, chemotherapy regimen and hormone.
NCCN, National Comprehensive Cancer Network.

guide clinical decision-making in the absence of patient-specific information. In the circumstance that a greater percentage of stage IV patients are luminal A, the ER testing can only be an option to increase the appropriate use of systemic therapy whilst keeping the cost for patients to a minimum. Only ER testing without evidence-based guidance of the actual prevalence in our region may compromise care in patients with luminal B but the limited access to HER2-directed treatments because of cost and inherent resistance of more than 50% of metastatic HER2-driven breast cancer towards anti-HER2 therapy may justify ER testing only in this setting.[10]

Therapeutic approaches for stage I–III were largely in agreement with the NCCN guidelines for chemotherapy use and endocrine treatments received in early disease with agreement rates of 1 (95% CI 0.91–1) and 0.81 (95% CI 0.65–0.92). This is because other major clinical prognostic factors were enough to drive the use of chemotherapy in this cohort. However, there was only slight agreement in the choice of chemotherapy regimen with an agreement scoring of 0.5 (95% CI 0.32–0.68). Chemotherapy combinations have evolved with specific regimens preferred for different subgroups. Most patients requiring adjuvant or neoadjuvant chemotherapy will benefit from taxane- and anthracycline-based regimens regardless of the molecular profile.[11] Based on the result of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, the NCCN panel excluded CAF as an option particularly in the adjuvant setting.[12] However, most patients in our study did receive CAF as an adjuvant or a neoadjuvant chemotherapy most likely because of the higher costs of taxanes. Although cisplatin is available and not costly, none of the patients with triple negative disease received platinum-based therapy which is an option in this subtype, highlighting the benefit for knowledge of receptor status prior to management.[13] Furthermore, BReast CAncer gene (BRCA) testing is not available in the public hospitals to assist in decision-making during treatment planning.

Important highlights from American Society of Clinical Oncology (ASCO) 2018 noted that 70% of early stage hormone-receptor-positive breast cancer with mid-range oncogene scores did not require chemotherapy as shown by the results from TAILOR X trial. Although a mere 10% of patients is in early stage of the disease, it is important to note that most of these patients with localised disease were hormone receptor positive. As local awareness programs advocate for strengthening screening, the proportion of patients in early stage of the disease is expected to rise. The costs and side effects associated with chemotherapy can be reduced when hormone receptor status and oncogene results are available. Hormone receptor status is, therefore, necessary and will have growing importance in guiding the choice of treatment in patients with local regional disease.

In contrast to stage I–III patients, poor agreement was observed for initial choice of therapy in stage IV patients. Patients with oestrogen-driven metastatic breast cancer, who would have been eligible for endocrine therapy as initial treatment, were prescribed chemotherapy. This may partly be because of the system-level delays and financial constraints in investigations to confirm visceral crisis as realised in other resource-constrained countries.[14] A lag period in accepting updated treatment guidelines which is not unique to Zimbabwe, but has been realised worldwide, is a probable factor.[15,16] Unavailability of hormone receptor results because of cost is a challenge as one cannot follow the NCCN guidelines in the stage IV setting whose minimal requirements include these results. Limited evidence regarding the clinical outcomes in stage IV endocrine-driven breast cancer from sub-Saharan setting with the typical huge fungating breast lesion is a possible reason why clinicians shun endocrine therapy. Chemotherapy is probably a more enticing option in this circumstance as clinicians seek better objective response rates.[17] No studies directly comparing chemotherapy vs endocrine therapy (tamoxifen only) have been carried out in Africa. In most instances, only tamoxifen is available. Favourable outcomes from endocrine treatments including CDK4/6 inhibitors are inaccessible for most public patients who have to bear the direct costs of cancer care. Local guidelines are in development for the use of endocrine treatments in the metastatic setting. Multidisciplinary meetings have been invaluable learning platforms for clinicians, from how to adopt latest guidelines, strategies to enable receptor testing on biopsy samples before referral to oncology units and strong consideration for endocrine therapy when appropriate in the metastatic setting, when appropriately coordinated, will inevitably reduce costs to patients. Clinical trials must be encouraged to generate local evidence to give clinicians confidence in choosing treatment strategies.

National Comprehensive Cancer Network does not routinely recommend combination chemotherapy in stage IV patients because of the small survival benefit and single-agent chemotherapy is preferred, if indicated. In our study, only 18% (6 of 33) of the stage IV patients who were recommended to receive chemotherapy had single agent prescribed as the first line, which is discordant with the NCCN recommendations.[17] This may be because of the fact that in our setting, stage IV patients are usually treatment naive with good marrow reserves and good performance status which may support clinicians prioritising higher objective response rates with reasonably acceptable toxicity. Notwithstanding these considerations, as literature outlines, treatment of stage IV patients should enhance the quality of life and therefore treatments associated with minimal toxicities like endocrine and targeted therapies are preferable for eligible patients.[4] Chemotherapy is more expensive at US$300 per cycle compared to tamoxifen which costs US$20 for a month's supply, and management of chemotherapy-associated side effects further compounds the expenses. Taken together, the over-utilisation of chemotherapy could be considered inappropriate use of limited resources.

The median time to results of receptor status availability was 8 months, a pattern which confirms the challenges encountered in retrieving receptor status results before

treatment decisions. Although most patients' results were not on time, three patients with stage III hormone-receptor-positive disease obtained their results by 3 months and therefore received hormone therapy on schedule. Amongst the challenges of untimely processing of results, poverty is the most likely reason as noted in other African studies.[18] Although some studies highlight poor pathology services, this is not the case in our set up as laboratories are highly competent but requires payment upfront, which most patients cannot afford at the time of diagnosis when other costs dominate the financial burden.[19] This is an important finding as patients with localised disease who obviously require chemotherapy can be encouraged to pursue hormone status and have the results by the end of chemotherapy without a negative impact on treatment. This will assist in minimizing financial burden as costs are spread and care is optimised.

Because the five patients who received the best supportive care with no cancer-specific therapy all turned out to be luminal A, there may be a need to consider empirical utilisation of endocrine therapy if the receptor status is unknown in such individuals. Hormone therapy has limited toxicities and can be prescribed as the cancer-directed treatment in such circumstances.

Although the NCCN guidelines recommend aromatase inhibitors for postmenopausal patients, the erratic supply and costs of aromatase inhibitors justify the widespread tamoxifen use in all breast cancer patients regardless of menopausal status in this setting. Research has shown a modest benefit of aromatase inhibitors compared to tamoxifen in reducing the risk of recurrence with no difference in the overall survival in postmenopausal specifically early stage, hormone-receptor-positive breast cancer as shown in both ATAC trial and BIG 1–98 trials recording similar hazard ratios.[20]

Our study has certain limitations including the small sample size, selection bias because of necessary exclusions, the retrospective study design and our findings are from a single institution data. However, to our knowledge this is the first study examining concordance to NCCN guideline recommendations based in Zimbabwe and will provide a useful data set for future comparison.

Conclusion

Treatment approaches were largely in agreement for stage I–III patients with reference to the NCCN guidelines. There was discordance in therapeutic approaches for stage IV patients with a preference for chemotherapy, the use of multidrug regimen when hormone profile is unknown at the time of treatment decision-making. It is critical for measures to be put in place in order to have molecular profiling results available at initial presentation as is universally recommended to aid in decision-making concerning definitive management.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

All authors contributed equally to this work.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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