

Research Paper

Value of glycated hemoglobin in the diagnosis of diabetes and prediabetes in cancer patients

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Abstract

Glycated haemoglobin (HbA1c) level is now recognized a diagnostic tool for diabetes and prediabetes. Cancer patients constitute risk group for these conditions. A five-month hospital-based cross-sectional study was carried out in the town of Douala, aiming to determine the prevalence of diabetes and prediabetes in cancer patients, evaluate the diagnosis performance of HbA1c and identify factors underlying its performance. Questionnaire and medical records were used to document patients' data and venous blood was collected to measure fasting plasma glucose (FPG) and HbA1c level. Haemoglobin count was also performed. In total, 172 women were enrolled and grouped into cervical cancer cohort (CCC, n =74), breast cancer cohort (BCC, n = 69) and control cohort (CC, n = 29). Based on FPG results, the prevalence of diabetes and prediabetes were 17.6 % and 13.5% respectively in the CCC, 20.3% and 10.1% in the BCC, 17.2% and 24.1% in the CC ($p < 0.05$). The prevalence of anaemia in these groups was 85.1%, 71.0% and 62.1% respectively ($p = 0.0259$). The sensitivity of HbA1c was 53.8% and 85.7% in CCC and BCC respectively while the specificity was 93.4 % and 90.8 % respectively. Agreement between HbA1c and FPG results was excellent in the CC but moderate CCC and BCC. Our findings suggest that HbA1c should not be recommended for the diagnosis of diabetes in cancer patients.

Keywords: Glycated haemoglobin, cancer patients, diabetes and prediabetes, diagnosis performance, Cameroon

Introduction

Breast and cervical cancers are the leading cause of cancer-related deaths among women especially in developing countries. In 2012, 1.7 million breast cancer cases were recorded with subsequent 521,900 deaths around the world, accounting for 25% of all cancer cases and 15% of all deaths from cancer in females. Cervical cancer is the second most diagnosed cancer and third leading cause of death from cancer among females in developing countries, about 527,600 cases and 265,700 subsequent deaths were recorded in 2012^[1]. In Cameroon, data on cancer are also a case for concern. GLOBOCAN (2012) statistics concerning Cameroon present an age-adjusted rate of cancer deaths of 73.1/100,000 persons/year and a risk of fatal outcome for any type of cancer prior to the age of 75 of 11%. Breast and cervical cancers are the most prevalent types of cancer among Cameroonian female population. Age-adjusted incidence and mortality rates are 27.9 and 16.6/100,000 persons/year respectively for breast cancer meanwhile for cervical cancer, they are 24 and 19/100,000 persons/year respectively^[2,3].

Diabetes mellitus (DM) is also a public health concern worldwide. According to the International Diabetes Federation (IDF), an estimated 280 million people live with diabetes of whom 13.6 million

are in Africa^[4]. Cancer and diabetes are diagnosed in the same individual more frequently than would be expected by chance, even after adjusting for age. The biological link between cancer and diabetes is complex and not entirely understood so far. Some authors pointed out an increased risk of certain cancers in diabetic patients^[5, 6]. On the other hand, other studies outlined a reverse causality. In fact, almost all organs may be affected by cancer disease *per se* and/or its treatment, the main complications including infections, electrolytic and metabolic disorders. Cancer patients thus present increased risk of developing diabetes and its complications^[7-10].

Early and accurate detection of diabetes and prediabetes among is critical. Diagnosis of diabetes relies mainly on glucose-based tests (fasting plasma glucose and oral glucose tolerance test) in most developing parts of the world. However, these tests have some limitations such as cost, patient preparation or considerable day to day variation of blood glucose, which therefore undermine their optimal use in clinical practice^[11-13]. The potential clinical utility of others diagnosis index, particularly glycated haemoglobin (HbA1c), was first mentioned in the 1985 WHO report. Two decades later, an international expert committee published a report advocating for the use of HhbA1c test to diagnose DM with the endorsement of several international societies^[14-15]. Glycated haemoglobin results from a combination of group of glucose or others hexoses (covalently linked) with the amino-terminal valine of the β -chain of haemoglobin, a protein contained in red blood cells^[12]. It is used as gold standard for monitoring glycaemia in diabetic patients. Methods using HbA1c can be performed at any time of the day and do not require the preparation of the patient. Furthermore, HbA1c provides for more revealing information on glycaemia than glucose-based methods since it depicts glycaemic history over the 3 to 4 previous months^[11-13]. Besides, studies consistently demonstrated a better correlation between diabetes-induced complications and HbA1c, compared with fasting glucose levels^[12]. Glycated haemoglobin might be good for early detection of diabetes in people at high risk^[16] such as cancer patients. Glycaemic control in cancer patients seems critical as some reports showed an increased mortality risk associated to diabetes in this group^[17,18].

Hence, the aims of this study were to determine the prevalence of diabetes and prediabetes in Cameroonian cancer women attending a health care facility, to investigate the impact of HbA1c criteria to diagnose prediabetes and diabetes by evaluating its diagnosis performances, and to analyze phenotypic characteristics of participants with discordant results at both tests in order to identify specific variables that might determine such a result and therefore help to direct the choice of the most appropriate diagnostic test.

Materials and Methods

This was a cross-sectional study carried out from May to September 2015 at the Douala General Hospital (Douala, Littoral Region, Cameroon). Patients were recruited at the cobaltotherapy and oncology units where they were treated as well as at the haematology and biochemistry units of the clinic biology laboratory where laboratory procedures were made. The study population consisted of women aged 21 years old and above who consented to participate in the study and signed an informed consent form. They had been diagnosed with cancer disease (cervical or breast) or were apparently healthy. Women with DM prior to their cancer disease, women presenting with a cancer disease other than cervical or breast cancer and women having refused to participate in the study were not included. Each woman was approached, the aim and objectives were clearly explained to each and answers were given to her questions. A total of 172 women were enrolled in the study and divided into three groups: 74 women with cervical cancer, 69 with breast cancer and 29 apparently healthy (control group). These three groups are referred to as cervical cancer cohort (CCC), breast cancer cohort (BCC) and control cohort (CC) respectively, later in this paper.

A structured questionnaire was administered for 10-15 minutes through standardized interview and medical records were consulted in order to document socio-demographic (age, residence area), anthropometric (height and weight), clinical (type of cancer, nature of treatment, number of rounds, diseases such as diabetes or kidney failure, tobacco smoking and alcohol drinking) data of participants. Weight and height were used to compute the body mass index (BMI) of women through standard BMI disc.

Four milliliters (4 mL) of blood was collected by venipuncture in EDTA tubes for the determination of glycated haemoglobin (HbA1C) and Full Blood Count. Blood was also collected into oxalate fluoride tubes for the determination of fasting glycaemia. Previous to blood sampling, all tubes were labelled

with patient's defined barcode. After sampling, the tube was gently shaken in order to avoid haemolysis and the appearance of air bubbles. Blood samples were then transported to the clinical biology laboratory of the hospital in cold box containing ice packs. Blood samples were collected only in fasting women, those not fasting were given a new appointment for blood sampling.

Blood samples collected in oxalate fluoride tubes were centrifuged (Rotaflex™, Germany) at 3500 rpm for 5 minutes and 500 µL of the serum was transferred into Eppendorf tubes and stored at -20°C until used. The determination of fasting glycaemia was done not more than three days after the blood sampling. Glycaemia was measured by a glucose oxydase (GOD)-based enzymatic colorimetric method using a semi-automated spectrophotometer (VISUAL™, Biomerieux, France), following the manufacturer's instructions. The apparatus was calibrated and standardized using negative and positive controls before analysis of sample. Measurement of glycaemia was done at 505 nm wavelengths^[19].

EDTA tubes containing blood samples were removed from the fridge (4°C) and left at room temperature (37°C) for 10 minutes. After haemolysis, glycated haemoglobin was measured based on turbidimetric inhibition immunoassay (TINIA) performed with a Cobas c311™ automate (Roche Hitachi, Japan) following manufacturer's instructions. This was aligned with International Federation of Clinical Chemistry standardization, according to Diabetes Control and Complications Trial/United Kingdom Prospective Diabetes guidelines. Most of samples (90 %) were analysed on the day of collection, the others (10%) were analysed not more than 4 days after collection.

Haemoglobin concentration was obtained through full blood using a flow cytometry-based technique (Cell Dyn Ruby, Abbott diagnostics, USA). The results were displayed on a screen for interpretation and exploitation. This analysis was performed within five hours following blood sampling, at the haematology unit of the clinical biology laboratory of the Douala General Hospital.

Based on BMI, haemoglobin, plasma glucose and HbA1c results, the participants were grouped in the following categories^[14, 16, 20]: Underweight: women with BMI < 18.5 Kg/m²,

- Normal weight: women with 18.5 Kg/m²<BMI < 25.0 Kg/m²,
- Overweight: women with 25.0 Kg/m²<BMI < 30.0 Kg/m²,
- Obesity: women with 30.0 Kg/m²<BMI < 40.0 Kg/m²,
- Morbid obesity: women with BMI > 40.0 Kg/m²,
- Anaemia: women with Hb<12.0 g/dL
- Prediabetes: women with fasting plasma glucose fitting in the]1.10-1.26 g/L[or HbA1c fitting in the [5.7 % -6.4 %] range
- Diabetes: women with fasting plasma glucose ≥ 1.26g/L or HbA1c ≥ 6.5 %.
- Non-diabetes: women with fasting plasma glucose ≤1.10 g/L or HbA1c< 5.7 %.

This study was carried out according to the guidelines for human experimental models in clinical research as stated by the Cameroon Ministry of Public Health. Besides, the ethical and administrative clearances for this study were issued by the institutional ethic committee of the University of Douala (N° CEI-UD/267/2015/M) and ethical committee of Douala General Hospital (N° 147 AR/MINSANTE/HGD/DM/2015). The aim and objectives of the study were explained to participants in the language they understood best (French or English), and their questions were answered. Only women who signed an informed consent form for their participation were enrolled. Participation in the study was strictly voluntary and women were free to decline answering any question or totally withdraw if they so wished at any time. Furthermore, there was no difference in the cancer related care provided to women who accepted to participate in the study and those who did not.

All data were verified for consistency, coded, and keyed in an Excel sheet. Thereafter, statistical analyses were performed with SPSS 20.0 for Windows (SPSS, Chicago, IL, USA). Data were summarized in table as percentages with 95% confidence interval (95%CI) or mean ± standard deviation (SD) for qualitative and quantitative variables respectively where appropriate. One way analysis of variance (ANOVA) or Mann-Whitney test were used to compare differences for normally-distributed variables. Chi-square test (χ^2) or Fisher's exact probability were computed to compare categorical variables. The agreement between fasting glycaemia and glycated hemoglobin methods was assessed by computing the Cohen's Kappa index^[21]. Its interpretation was made based on the scale by Landis and Koch (1977) who splitted the kappa index into five categories namely very poor

(<0.00), poor (0.00-0.20), moderate (0.21-0.60), good (0.61-0.80) and excellent (≥ 0.81)^[22]. Significant levels were measured at 95% CI with significant differences recorded at p -value < 0.05.

Results and Discussion

Characteristics of the study population

A total of 172 women included in the study, 74, 69 and 29 in cervical cancer group, breast cancer group and control group respectively. The baseline characteristics of the three cohorts are summarized in table 1. Overall, cancer patients were significantly older than apparently healthy patients ($p < 0.0001$). On the other hand, haemoglobin level and proportion of smokers were lower in both cancer groups ($p < 0.0001$ and $p = 0.0002$ respectively). Proportion of patients under cancer therapy was significantly higher in the breast cancer group (91.3 % versus 77.1 % respectively, $p = 0.00235$) (Table 1).

Table 1: Characteristics of the population

Parameters	Cervical cancer cohort n = 74	Breast cancer cohort n = 69	Control cohort n = 29	P-value
Age (years)	52.2 \pm 11.2	49.2 \pm 10.6	36.6 \pm 13.3	< 0.0001
BMI (Kg/m ²)	26.867 \pm 5.155	29.325 \pm 6.078	29.132 \pm 6.145	0.0258
Obese (yes)	15 (20.3 %)	30 (43.5 %)	11 (37.9 %)	0.0100
Haemoglobin (g/dL)	9.850 \pm 2.171	11.368 \pm 1.494	11.483 \pm 1.318	< 0.0001
Red blood cells (10 ⁶ / μ L)	3.468 \pm 0.705	3.922 \pm 0.849	3.858 \pm 0.504	0.0009
FPG (g/L)	1.172 \pm 0.593	1.116 \pm 0.444	1.164 \pm 0.682	0.8178
HbA1c (%)	5.656 \pm 1.407	5.878 \pm 1.387	5.724 \pm 1.709	0.6535
Cancer therapy	77.1 %	91.3 %	-	0.0235
Smokers	8.1 %	14.5 %	44.8 %	0.0002
Physical activity (yes)	20.3 %	21.7 %	58.6 %	0.0002

BMI, Body mass index, FPG, Fasting plasma glucose, HbA1c, Glycated haemoglobin.

Data are expressed as mean \pm standard deviation or as percentage. Differences between groups were analyzed by one-way analysis of variance (ANOVA) for normally-distributed variables. Categorical variables were analyzed by the χ^2 -test. P-values < 0.05 are considered significant.

Prevalence of diabetes and prediabetes

Findings in this part were based on the results of fasting plasma glucose test considered as the gold standard for diagnosing diabetes and prediabetes. The prevalence of diabetes was 17.6% (13/74, 95% CI:10.1-28.5%), 20.3 % (14/69, 95% CI:11.9-32.0%) and 17.2% (5/29, 95% CI:6.5-36.5%) in the CCC, BCC and CC groups respectively ($\chi^2 = 0.218$, $ddl = 2$, $p = 0.8970$). Likewise, the prevalence of prediabetes in these groups were 13.5% (10/74, 95% CI:7.0-23.9%), 10.1% (7/69, 95% CI:4.5-20.4 %) and 24.1% (7/29, 95% CI:11.0-43.9%) respectively ($\chi^2 = 3.351$, $ddl = 2$, $p = 0.1870$).

Prevalence of anaemia

Overall anaemia was found in 130 of the 172 participants (75.6%, 95% CI:68.3-81.7%) in this study. The prevalence of anaemia was 85.1% (63/74, 95% CI: 74.5-92.0%), 71.0% (49/69, 95% CI: 56.7–80.9%) and 62.1% (18/29, 95% CI: 42.4-78.7%) in CCC, BCC and CC respectively and the difference was statistically significant ($\chi^2 = 7.308$, $ddl = 2$, $p = 0.0259$). As presented in the table 1, the mean values of haemoglobin were 9.850 \pm 2.171 g/dL, 11.368 \pm 1.494 g/dL and 11.483 \pm 1.318 g/dL respectively ($p < 0.0001$).

Agreement between HbA1c and FPG results

In cervical cancer cohort, 53.8 % of patients diagnosed as diabetic by FPG had a HbA1c ≥ 6.5 %. However, merely 30.0 % of prediabetic patients by FPG had HbA1c between 5.7 and 6.4 %. Results were more converging in normoglycemic patients as 82.3% of them had HbA1c less than 5.7 % (Table 2). Agreement was computed only with results from diabetes patients owing to more convenient sample size for. The agreement between HbA1c and FPG, in this cohort, was moderate ($\kappa = 0.503$, $p < 0.0001$) in diabetic patients.

In the breast cancer cohort, diabetic participants were better identified by HbA1c (85.7%) than prediabetic (28.6%) and normoglycemic participants (77.1%) respectively (Table 2). Agreement between both diagnosis methods was also moderate ($\kappa = 0.575$, $p < 0.0001$), though higher than in the cervical cancer cohort.

In the control cohort, results were 100%, 14.3% and 88.2% in diabetic, prediabetic and normoglycemic participants respectively (Table 2). An excellent agreement ($\kappa = 0.923$, $p < 0.0001$) between both methods was found.

Table 2: Prevalence of patients diagnosed by the fasting plasma glucose and glycated haemoglobin in the three studied cohorts

	HbA1c			Total
	< 5.7 %	5.7-6.4 %	≥ 6.5 %	
<i>Cervical cancer cohort</i>				
FPG				
Diabetesmellitus	2 (15.4 %)	4 (30.8 %)	7 (53.8 %)	13 (17.6 %)
Prediabetes	6 (60.0 %)	3 (30.0 %)	1 (10.0 %)	10 (13.5 %)
Normoglycemic	42 (82.3 %)	6 (11.8 %)	3 (5.9 %)	51 (68.9 %)
Total	50 (67.6 %)	13 (17.6 %)	11 (14.8 %)	74
<i>Breast cancer cohort</i>				
FPG				
Diabetesmellitus	0 (0.0 %)	2 (14.3 %)	12 (85.7 %)	14 (20.3 %)
Prediabetes	3 (42.8 %)	2 (28.6 %)	2 (28.6 %)	7 (10.1 %)
Normoglycemic	37 (77.1 %)	7 (14.6 %)	4 (8.3 %)	48 (69.6 %)
Total	40 (57.9 %)	11 (15.9 %)	18 (26.2 %)	69
<i>Control cohort</i>				
FPG				
Diabetesmellitus	0 (0.0 %)	0 (0.0 %)	5 (100 %)	5 (17.3 %)
Prediabetes	5 (71.4 %)	1 (14.3 %)	1 (14.3 %)	7 (24.1 %)
Normoglycemic	15 (88.2 %)	2 (11.8 %)	0 (0.0 %)	17 (58.6 %)
Total	20 (69.1 %)	3 (10.3 %)	6 (20.6 %)	29

FPG, Fasting plasma glucose, HbA1c, Glycated haemoglobin.

Diagnosis performances of HbA1c for diabetes

In cervical cancer cohort, HbA1c ≥ 6.5 % for the diagnosis of diabetes exhibited a sensitivity of 53.8 % (95%CI: 26.1-79.6 %), a specificity of 93.4 % (95%CI: 83.3-97.9 %), positive and negative predictive values of 63.6 % (95%CI: 31.6-87.6 %) and 90.5 % (95%CI: 79.8-96.1 %) respectively. Performances were better globally in breast cancer cohort with a sensitivity of 85.7 % (95%CI: 56.2-97.5 %), a specificity of 90.8 % (95%CI: 80.3-96.2 %), positive and negative predictive values of 66.7 % (95%CI: 41.2-85.7 %) and 96.7 % (95%CI: 87.6-99.4 %) respectively. These performances index were 100 % (95%CI: 46.3-100 %), 92.9 % (95%CI: 64.2-99.6 %), 83.3 % (95%CI: 36.5-99.1 %) and 100 % (95%CI: 71.7- 100 %) respectively in the control cohort.

Phenotypic characterization of patients with discordant results and associated factors

Discordant results were obtained between HbA1c and FPG in 27.9 % (48 women) when diagnosis of diabetic was performed (29.7%, 27.6% and 26.1% in CCC, BCC and CC respectively). Six types of discrepancies were recorded, namely normal fasting glycaemia versus HbA1c between 5.7-6.4 % (15 women, 31.2%), normal fasting glycaemia versus HbA1c ≥ 6.5 % (7 women, 14.5%), prediabetes versus HbA1c < 5.7 % (14 women, 29.2 %), prediabetes but HbA1c ≥ 6.5 % (4 women, 8.4 %), diabetes but HbA1c between 5.7-6.4 % (6 women, 12.5 %) and diabetes but HbA1c < 5.7 % (2 women, 4.2%).

Table 3: Comparison of characteristics of patients with respect to concordance or discordance between fasting plasma glucose and glycated haemoglobin in the three clinical groups

	Cervical cancer cohort			Breast cancer cohort			Control cohort		
	Concordant	discordant	P-value	Concordant	discordant	P-value	Concordant	discordant	P-value
Age (years)	52.3 ± 10.9	52.0 ± 12.0	0,922	48.6 ± 10.4	50.8 ± 11.3	0,4429	36.6 ± 14.6	36.4 ± 10.0	0,6776
BMI (Kg/m ²)	26.6 ± 5.6	27.6 ± 3.9	0,461	28.7 ± 5.9	31.0 ± 6.2	0,1657	29.6 ± 6.7	28.0 ± 4.6	0,9222
Obesity (Yes)	11 (21.2 %)	4 (18.2 %)	0.7695	20 (39.2 %)	10 (55.6 %)	0.5562	8 (38.1 %)	3 (37.5 %)	0.9998
Anemia (Yes)	45 (86.5 %)	18 (81.1 %)	0.7227	35 (68.6 %)	14 (77.8 %)	0.5562	16 (76.2 %)	2 (25.0 %)	0.0281
Physical activity (yes)	5 (9.6 %)	1 (4.5 %)	0.6624	10 (19.6 %)	0 (0.0 %)	0.0563	9 (42.9 %)	4 (50.0 %)	0.9998

BMI, Body mass index,

Data are expressed as mean ± standard deviation or as percentage.

Differences between groups were analyzed by Mann-Whitney test for not normally-distributed variables.

Categorical variables were analyzed by the Fisher's exact test. P-values < 0.05 are considered significant.

Discussion

The present study aimed to determine the prevalence of diabetes and prediabetes in Cameroonian cancer women attending a health care facility, to investigate the impact of HbA1c criteria to diagnose prediabetes and diabetes by evaluating its diagnosis performances; and to analyze phenotypic characteristics of participants with discordant results at both tests.

The FPG-based prevalence of diabetes and prediabetes were higher in cancer patients groups compared with the control group. This could be explained by the fact that cancer patients were significantly older and had less physical activity. This finding agrees with the literature which highlights that these factors aging and insufficient physical activity are associated with increased risk of diabetes^[5]. Besides, cancer therapy could also explain the higher prevalence of diabetes observed in cancer patients. Cisplatin-based chemotherapy alone or coupled with radiotherapy were the most provided therapeutic protocol in our patients (data not shown). Previous studies pointed out that cisplatin and cisplatin-like molecules could cause hyperglycaemia in diabetic and nondiabetic adults. This hyperglycaemia increases the risk of developing complications including grade 4 neutropenia, neutropenic fever, sepsis and neuropathy^[10]. The control of glycaemia in these patients is thus very important for preventing hyperglycaemia and consequently diabetes in the course of the management of cancer.

A moderate agreement was found between fasting plasma glucose and glycated haemoglobin for the diagnosis of diabetes in both groups of cancer patients despite acceptable sensitivity and specificity. This has been reported in other studies with different target populations^[16, 23]. Agreement was better in patients from the control group. This could be explained in part by differences related to sample size. We recorded a significantly higher prevalence of anaemia in cancer patients, compared with control patients. Anaemia is known to artificially reduce HbA1c values and thus, jeopardize its performance as a diagnosis tool for diabetes^[14]. Any condition as anaemia, hemoglobinopathies, hemolysis, recent transfusion nor chronic renal failure can shorten red blood cells survival, thus hindering the optimal use of HbA1c for the diagnosis of diabetes and prediabetes. As outlined by D'Emden^[13] on the behalf of the Australian diabetes society, if any of the aforementioned conditions exists, the diagnosis should be made through measure of blood glucose. Thus, oncologists and other healthcare providers should be aware and knowledgeable about the limitations of HbA1c as diagnostic tool for diabetes, though it has many advantages making it very attractive. Anaemia in cancer patients is mainly due to the disease itself and its therapy^[7]. In addition, impaired renal function has also been reported in cervical cancer women receiving cisplatin-based therapy (Assokom and colleagues, personal communication). This is also a condition that may have a negative influence on the diagnosis performance of HbA1c^[12, 13]. The prevalence in of anaemia the control group was high, thought lower than in cancer patients groups. This could be due to others anaemia-inducing comorbidities such malaria which is highly prevalent in Cameroon^[24]. These results underscore a mitigated clinical utility of HbA1c as a diagnosis tool for diabetes and prediabetes in cancer patients. Considering our somewhat small sample size, more studies on the topic with larger sample size are needed to confirm or infirm our assumption since it was unpractical to assess the performance of HbA1c to diagnosis prediabetes and the phenotypic peculiarities of persons with discrepant results. Moreover, further studies on anaemia, hemoglobinopathies and others factors that might have an influence on HbA1c levels are needed in our context, in order to better depict the clinical utility of HbA1c for the diagnosis of diabetes. Our results are derived from single blood measurements, reflecting what is done in routine medical practice in most health facilities of resources-limited countries.

Conclusion

The prevalence of diabetes and prediabetes was higher in cancer patients. The agreement between HbA1c and FPG for the diagnosis of diabetes was moderate in cancer patients and excellent in control groups, though a significant proportion of anaemic patients were recorded in all three groups. Our findings suggest that HbA1c should not be recommended for the diagnosis of diabetes in cancer patients. Nonetheless, further studies are needed to confirm or infirm this assumption in our context. Clinicians and other health providers should be aware and knowledgeable about the limitations of HbA1c as a diagnostic tool for diabetes and prediabetes in cancer patients, despite its numerous advantages.

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