ORIGINAL RESEARCH

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The Impact of Hybrid Capture-Based Comprehensive Genomic Profiling on Treatment Strategies in Patients with Solid Tumors

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ABSTRACT Objective: Sleep quality (SQ) can be steady decline in the of breast cancer patients after treatment. The aim of this study was to assess the SQ of breast cancer patients treated with Cyclin-dependent kinase (CDK) 4–6 inhibitor plus endocrine therapy (ET). **Material and Methods:** The data were collected from three different cancer centers. Eighty consecutive patients were included in this study. The Pittsburg Sleep Quality Index(PSQI) was employed for the assessment of the SQ in metastatic breast cancer patients after receiving treatment with CDK4–6 inhibitors plus ET for at least three months. **Results**: The PSQI scores revealed that 68.8% of patients treated with CDK4–6 plus ET have poor SQ. The mean score of the PSQI was 8 (ranging from 1-17). Univariate analysis was employed, revealing a significantly higher sleep latency (p= 0.024), sleep disturbance (p= 0.011), and daytime dysfunction (p= 0.012) in patients receiving letrozole as compared to patients treated with Fulvestrant. Similarly, the mean score of the PSQI was also higher in letrozole-treated patients in comparison with Fulvestrant-treated patients (p= 0.042). The multivariate analysis revealed a significantly higher rate of daytime dysfunction in letrozole-treated patients as compared to Fulvestrant-treated patients (The odds ratio was 0.51, 95% confidence interval(CI), 0.30 to 0.86; p=0.008). In addition, no significant difference was observed in the sleep quality of patients receiving either Ribociclib or Palbociclib. **Conclusion:** The study evidently shows a worsening of SQ in patients receiving letrozole in comparison with patients receiving Fulvestrant. CDK4–6 inhibitors have a similar effect on SQ.

Keywords: Comprehensive genomic hybridization; genomics; neoplasms; retrospective studies

In recent decades, considerable progress has been made in understanding the molecular pathways of tumor progression and development.[1] Treatment strategies for major cancer types have been transformed by the identification of a key mutation that is known as “driver mutation” present in a molecular pathway.[2] For instance, anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR)

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in lung cancer or B-RAF inhibition in melanoma have significantly changed our way to the treatment of these tumors.[3] This has led to a rising interest in precision medicine and has made it increasingly evident to most physicians that interventions in oncology have shifted from histology-based treatment protocols to histology-agnostic treatment protocols based on the driver mutations.[4] However, so far, the US Food and Drug Administration (FDA) has approved tumor agnostic treatments only for patients with tumor mutational burden-high (TMB-H), microsatellite instability-high, and neurotrophic tyrosine receptor kinase fusion-positive tumours.[5]

Recently, Comprehensive Genomic Profiling (CGP) has become more popular among oncology practitioners. CGP is a next-generation sequencing (NGS) approach that detects novel and known variants for the four main classes of genomic alterations (GA) and signatures. It provides prognostic, diagnostic, and predictive insights for all cancer types, which in turn aids in personalized research or treatment decisions for patients.[5] Moreover, in oncology, master protocols (basket, umbrella trials with or without adaptive clinical trials) aiming to compare the effectiveness of matched treatment with standard treatment protocols are encouraged by the FDA, National Cancer Institute, and European Society for Medical Oncology (ESMO).[6] In 2019, there were 89 basket trials on a wide range of tumor types to define the role of tumor-agnostic molecular-based treatment approaches.[6] However, the integration of CGP with molecularly guided treatment into the routine oncology practice still poses a challenge due to several practical and financial limitations. In literature, there is scarce data available on how CGP results impact and change the treatment approach in cancer patients.[2,7] Therefore, we aimed to evaluate the non-CGP/hotspot testing and to identify the GAs and matched therapies or suitable clinical trials based on the hybrid capture-based CGP report. We also investigated the impact of CGP on the treatment plan in a significant number of patients with advanced-stage solid tumors.

MATERIAL AND METHODS

The research was designed as a multicenter, descriptive (observational), and retrospective cohort study. All patients with advanced solid tumors whose CGP reports were reviewed by a physician prior to enrollment and who were followed up and treated between January 2015 and December 2019 at 15 participating centers were included. Patients, who did not provide informed consent for the use of their medical data, were excluded (except for the patients who were deceased). Statistical analysis included 164 patients who met all inclusion criteria. The study was approved by the Ethical Review Committee of the Cerrahpaşa Faculty of Medicine at İstanbul University (date: June 18, 2019, no: C-03) and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Medical records of eligible patients were reviewed on admission or first presentation for their type of cancer, lines of previous chemotherapy, number of prior treatments, the result of hybrid capture-based CGP, the number of actionable mutations defined by hybrid capture-based CGP, list of approved drugs for diseases, and potential eligibility for any clinical trials worldwide. In addition, the treatments used after genomic profiling were also listed.

For statistical analysis, descriptive methods were used, with numerical variables being reported as mean with standard deviation (SD) or median with interquartile range (IQR) and categorical variables as the frequency with percentage.

RESULTS

In total, 166 patients with a histologically confirmed diagnosis of malignant tumor were found eligible for the study. Statistical analysis included 164 patients who met all the inclusion criteria. 114 (69.5%) patients died before the time of data analysis. Among all patients, 82 (50%) were male, and the mean age was 55.3 (SD±14.4) years. The overall clinical and demographic characteristics of the patients are presented in Table 1. The patients with a diagnosis of non-small-cell lung carcinoma (NSCLC), breast cancer, carcinoma of unknown primary (CUP), colorectal carcinoma and sarcoma represented 61.5% (n=101) of all cases, including 33 (20.1%), 25 (15.2%), 17 (10.4%), 14 (8.5%), and 12 (7.3%) patients, respectively (Table 2).

TABLE 1: Demographics and baseline characteristics.

		Total n (%)	NSCLC	Breast	Unknown primary carcinoma	Colorectal carcinoma	Sarcoma	Pancreatic	Stomach	Other
Gender	Male	82 (50)	23 (69.7%)	0 (0.0%)	9 (52.9%)	9 (64.3%)	7 (58.3%)	7 (77.8%)	6 (66.7%)	21 (46.7%)
	Female	82 (50)	10 (30.3%)	25 (100.0%)	8 (47.1%)	5 (35.7%)	5 (41.7%)	2 (22.2%)	3 (33.3%)	24 (53.3%)
Age	Median (IQR)	55.0 (45-66)	61.0 (52-65)	51.0 (42.5-58)	56.0 (46.5-63.5)	53.0 (47-65)	43.0 (31-66.8)	70.0 (53-75.5)	59.0 (44-66)	54.0 (40-6)
	Mean (SD)	55.3±14.4	59.5±11.1	51.0±10.6	56.5±13.4	54.6±11.9	46.8±18.2	65.8±13.6	55.1±14.7	54.4±16.8
Patient status	Alive	50 (30.5)	8 (24.2%)	6 (24.0%)	6 (35.3%)	3 (21.4%)	5 (41.7%)	1 (11.1%)	2 (22.2%)	19 (42.2%)
	Dead	114 (69.5)	25 (75.8%)	19 (76.0%)	11 (64.7%)	11 (78.6%)	7 (58.3%)	8 (88.9%)	7 (77.8%)	26 (57.8%)

NSCLC: Non-small-cell lung carcinoma; IQR: Interquartile range; SD: Standard deviation.

TABLE 2: Histology of tumors (n=164).

Diagnosis	Frequency	Percent
NSCLC	33	20.1
Breast	25	15.2
Unknown primary carcinoma	17	10.4
Colorectal	14	8.5
Sarcoma	12	7.3
Pancreatic	9	5.5
Stomach	9	5.5
Others	45	27.4
Total	164	100.0

Others: Ovary, hepatobiliary carcinoma, head and neck, melanoma, uterus, brain, neuroendocrine, prostate, SCLC, bladder carcinoma, cervix squamous cell carcinoma, epidermoid carcinoma, kidney, larynx, nasopharynx, and paranasal, small intestine, testis; NSCLC: Non-small-cell lung carcinoma.

In total, 44 positive GAs were detected by local genomic testing [polymerase chain reaction, fluorescence in situ hybridization (FISH)-chromogenic in situ hybridization, and hotspot gene paneling] in the study group (Table 3).

TABLE 3: Positive genomic markers detected by classical diagnosis methods.

	n	Percent (in 164 patients)
ALK	3	1.8
BRAF	7	4.3
EGFR	8	4.9
PDL1	4	2.4
ROS	2	1.2
HER2 FISH	5	3.0
KRAS	9	5.5
MSI	2	1.2
Other	4	2.4
Total	44	26.8

Some patients had more than one record; ALK: Anaplastic lymphoma kinase; EGFR: Epidermal growth factor receptor; FISH: Fluorescence in situ; MSI: Microsatellite instability-high.

CGP test was performed with a median of 13.7 (IQR, 4.4-30.4) months following the diagnosis of advanced cancer. It was performed at baseline in 13 patients (7.9%) and after the first-, second-and third-line of systemic therapy in 72 (43.9%), 24 (14.6%), and 55 (33.5%) patients, respectively.

Figure 1 shows the frequencies of GAs detected by CGP according to tumor types. The most common GAs were TP53, KRAS, CDKN2A/B, PIK3CA, and MYC. According to the CGP report, at least one GA was found in 158 (96.4%) patients. In total, 633 gene alterations were detected among 164 patients. The mean number of alterations per patient was 3.5 (SD±2.0) [median 3.5 (IQR 2.0-5.0)].

Among all patients, the mean TMB was 7.3 (SD±8.7) mut/Mb. However, it was higher than 10 mut/MB in 32 (22.4%) patients, which was also clinically relevant. In NSCLC patients, TMB≥10 10 mut/MB was 53.8%, which was substantially higher compared to other tumor types, although the mean TMB in NSCLC was 10.4 (SD±7.1) mut/Mb (Table 4). However, all the patients were microsatellite stable.

CGP reports of the patients analyzed showed that 58 patients had 79 evidence-based drug suggestions for their tumor type, whereas 97 patients had 153 evidence-based drug suggestions for another tumor type. Moreover, at the time of the study, 126 (76.8%) patients were potentially eligible for 267 actively recruiting clinical trials.

The treatment strategies used after the CGP test can be classified as chemotherapy, targeted therapy, and immunotherapy with a rate of 79.1%, 15.2%, and 15.9%, respectively. After interpretation of the CGP

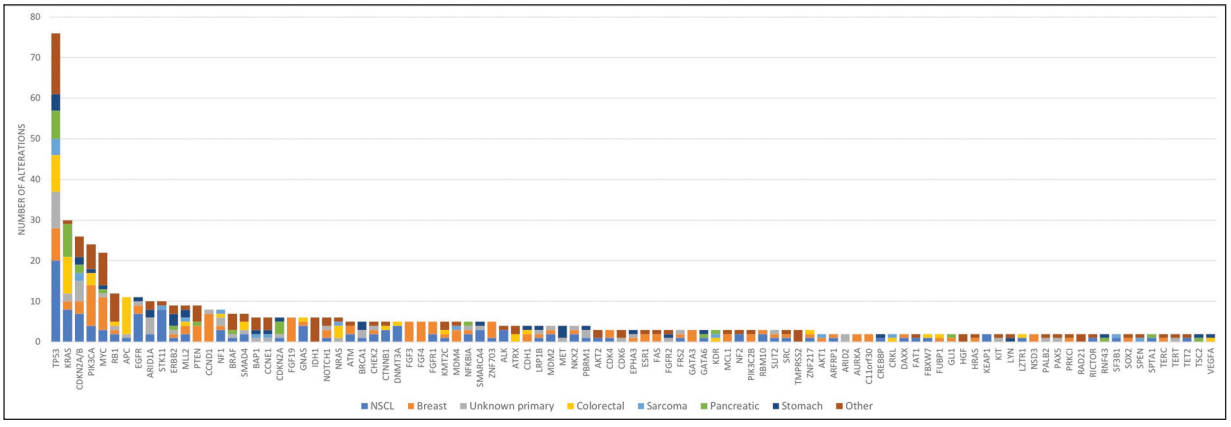

FIGURE 1: The distribution of genomic alterations according to tumor types (genes altered in a single sample are not shown).
NSCLC: Non-small-cell lung carcinoma.

TABLE 4: High TMB rates in different tumor types.

		TMB≥10
Diagnosis	**n**	**%**
NSCL (n=26)	14	53.8
Breast (n=24)	2	8.3
Unknown primary (n=15)	2	13.3
Colorectal (n=13)	2	15.4
Sarcoma (n=12)	1	8.3
Pancreatic (n=5)	1	20.0
Stomach (n=8)	3	37.5
Other (n=40)	7	17.5
Total (n=143)	32	22.4

TMB: Tumor mutational burden; NSCLC: Non-small-cell lung carcinoma.

by the primary oncologist, substantial changes were made in the treatment decisions of 35 (21.3%) patients. We found that the chemotherapy had a proportion of 88.8% in the treatment lines prior to CGP, and it was reduced to 79.1% following CGP, while the proportion of targeted therapy increased from 11.3% to 15.2% and immunotherapy from 4.2% to 15.9%. A Sankey diagram in Figure 2 shows the change in treatment regimens after the CGP test.

DISCUSSION

A study by De Falco et al. reported that CGP was performed at baseline and after the first-line treatment in 20% and 50% of the patients, respectively.[4] In our study, CGP was performed in 7.9% and 43.9% of the patients at baseline and during second-line treatment, respectively. It appears that physicians in Türkiye perform CGP less frequently at the baseline compared to their Italian colleagues, which can be attributed to several factors. First, the samples were sent at the discretion of the patient's primary physician, and thus the results could not be representative of the general population. Second, in Türkiye, the hotspot gene NGS is more accessible and affordable than CGP. Therefore, we believe that most of the clinicians in Türkiye first try to perform local NGS with hotspot gene panel and then perform the CGP in patients with negative or inconclusive outcomes. On the contrary, these results also showed high motivation of the medical oncologist in Türkiye to find an effective druggable target prior to the second-line cytotoxic chemotherapy.

In our study, at least one GA was found in 158 (96.4%) patients with a median of 3.5 (IQR 2.0-5.0) GA per patient. The studies by Wheler et al. and Frampton et al. reported that it was 5 and 3.06 (0-23), respectively.[8,9] In addition, multiple studies with patients with different tumors have also reported detection of at least one GA in 82.1-93.5% of the cases by CGP test.[4,8,10] The most common GAs detected by CGP were TP53 (46.3%), KRAS (18.3%), CDKN2A/B (15.9%), PIK3CA (14.6%), and MYC (13.4%). Unfortunately, most of these mutations are not druggable targets compared to EGFR, ALK, or BRAF mutations. Additionally, Fumagalli et al. reported that when they performed CGP in patients with NSCLC, they found at least one GA in 87% of their 76 patients.[11] In our study, although targeted mutations were detected in 31/164 (18.9%) patients [EGFR (4.9%), BRAF (4.3%), KRAS (3.0%), PDL1

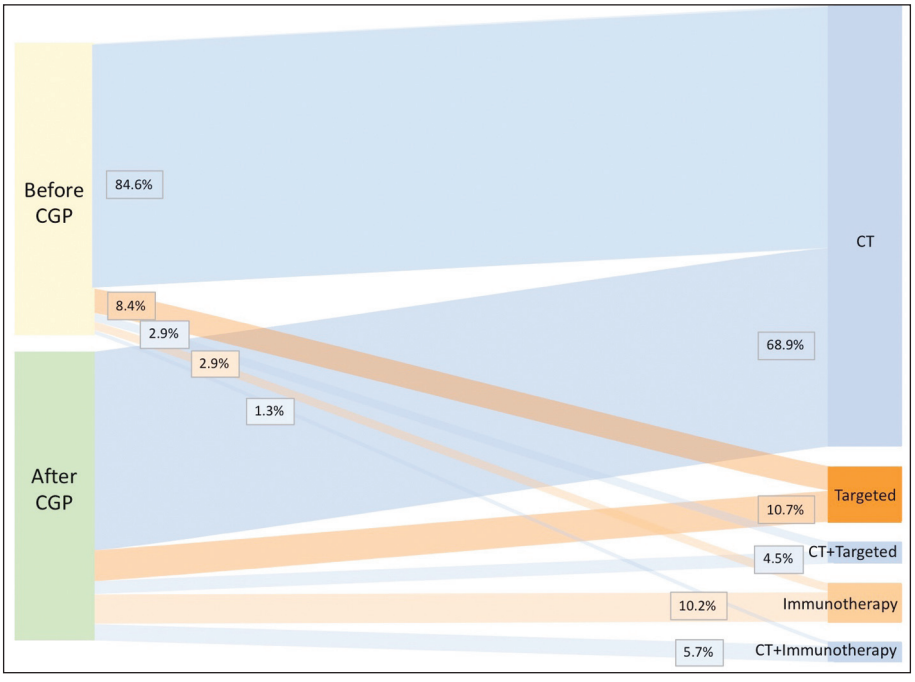

FIGURE 2: Treatment regimens before and after the CGP testing.
CT: Chemotherapy; CGP: Comprehensive genomic profiling.

(2.4%), HER2 FISH (2.4%), and ALK (1.8%)] using classical methods, a further genomic examination was required in these patients. For this reason, it would be more reasonable to conduct CGP for the patients at the baseline.[12] In a report of ESMO Precision Medicine Working Group, which presents its recommendations on the use of NGS for patients with metastatic cancer, it is recommended to use tumor multigene NGS, especially in patients presenting with advanced NSCLC, prostate, ovarian cancers, and cholangiocarcinoma.[12]

Our genomic profiling results revealed 79 evidence-based drug suggestions for the patients' tumor type and 153 evidence-based drug suggestions for another tumor type in 58 (35.4%) and 97 (59.1%) patients, respectively. After interpretation of the CGP by the primary oncologist, significant changes were made in treatment strategies in 35 (21.3%) patients. Drilon et al. reported that GA leads to major treatment changes in 26% of the patients, which was compatible with the National Comprehensive Cancer Network (NCCN) guideline recommendations.[13] In the literature, major treatment changes were reported in 21-45% of the cases after CGP.[7,14] In our study, the proportion of cytotoxic chemotherapy administered prior to CGP was 88.8%; this percentage decreased to 79.1% in the treatments given after CGP, whereas the proportion of targeted therapy increased from 11.3% to 15.2%. We strongly believe that this change is associated with increased detection of targetable driver mutations by CGP.

The overall percentage of patients with TMB≥10 muts/Mb was 22.4%, compared to 53.8% in NSCLC patients. Our results showed that TMB≥10 muts/Mb was detected in patients with gastric cancer, CUP, and sarcoma, with a mean value of 9.6 (SD±5.9) 7.5 (SD±15.3), and 7.3 (SD±11.8) muts/Mb, respectively. These tumors showed higher TMB compared to other histology in the study. TMB is a new biomarker for cancer immunotherapy. Since TMB has a positive correlation with the neoantigen load, it has been reported that high TMB is associated with increased anti-tumor immune responses and greater utilization of immune checkpoint inhibitors.[14] This relationship between TMB and immune-checkpoint inhibitors has led to the first tumor-agnostic drug approval by the FDA.[15] NCCN strongly recommends that each cancer patient with good performance sta-

tus and a lack of standard treatment options should undergo TMB testing to seek potential benefits from checkpoint inhibitors.[16]

Multiple studies using various profiling approaches have shown that molecular profiling-guided therapy may have significant benefits in terms of response rates and survival rates. Some studies used a single analytical approach (i.e., NGS), while others applied multiple analytical methods for extensive molecular profiling. Multiplatform profiling analyses could find more druggable molecular targets and guide a higher proportion of patients toward matched-treatment strategies.[17] In our study, due to the lack of effectiveness of data in our retrospective analysis, we could not reach a firm conclusion on the response rate and survival rate of our patients.

Our results provide conclusive evidence for the effectiveness of CGP in daily oncology practice using a relatively high number of patients in full datasets from Türkiye, which is a developing country. However, a few limitations are worth noting. First, patients were selected at the discretion of the patient's primary oncologist; thus, the results cannot be generalized. Second, the retrospective nature of the study without any comparison of CGP-based treatment with standard care in effectiveness parameters (response rate and survival rate) precludes us from drawing general conclusions. Third, there was no formal molecular tumor board to evaluate the result of the CGP and all treatment suggestions by the primary oncologist. Another limitation of the study is that there was no direct comparison with hot spot or single mutation testing, and we believe that it would be an interesting area for further research. On the other hand, our study had the strength to examine an extensive number of alterations at the same time using CGP.

CONCLUSION

In conclusion, our data showed that CGP identified GA in over 90% of cancer patients. Bioinformatics evaluation of CGP resulted in evidence-based drug options in patients' tumor type and another tumor type for 58 (35.4%) and 97 (59.1%) patients, respectively. Moreover, our study revealed that the treatment strategies changed after CGP in 35 (21.3%) patients. However, due to reimbursement issues in Türkiye, we could not use pembrolizumab in TMB-H patients. But we strongly believe that the affordability of the high-TMB or other tumor-agnostic drugs will significantly increase in the future, and CGP testing will serve as one of the major decision-making tools for the patients along with pathological, radiological, or laboratory tests.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Umut Dişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Sezer Sağlam, Mesut Şeker, Sercan Aksoy, İbrahim Tek, Yeşim Eralp, Nil Molinas Mandel, Gökhan Demir, Çağatay Arslan, Mutu Demiray, Taflan Salepci, Mehmet Akif Öztürk, Fatih Selçukbiricik, Gökçe Temizaş, Ebru Gül Fidan;* ***Design:*** *Umut Dişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Sezer Sağlam;* ***Control/Supervision:*** *Umut Dişel, Fatih Köse, Ahmet Bilici;* ***Data Collection and/or Processing:*** *Umut Dişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Sezer Sağlam, Mesut Şeker, Sercan Aksoy, İbrahim Tek, Yeşim Eralp, Nil Molinas Mandel, Gökhan Demir, Çağatay Arslan, Mutlu Demiray, Taflan Salepci, Mehmet Akif Öztürk, Fatih Selçıkbiricik;* ***Analysis and/or Interpretation:*** *Umut Sişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Sezer Sağlam;* ***Literature Review:*** *Umut Sişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Sezer Sağlam;* ***Writing the Article:*** *Umut Dişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Gökçe Temizaş, Ebru Gül Fidan;* ***Critical Review:*** *Umut Dişel, Fatih Köse, Ahmet Bilici, Mustafa Özgüroğlu, Gökçe Temizaş, Ebru Gül Fidan;* ***References and Fundings:*** *Gökçe Temizaş, Ebru Gül Fidan.*

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