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Molecular Profiling for Patients with Solid Tumors: A Single-Institution Experience

Keywords: Cancer; Neoplasm; Genomic profiling; Tumor profiling; Survival

Abstract

Molecular Profiling (MP) of tumors is innovative progress that led to identifying targetable alterations that could be exploited to deliver personalized cancer treatment. Lack of data from the region about the clinical utility of has prompted this study. Tumor tissues from 100 consecutive adult patients with solid tumors were genomically profiled successfully using commercially available platforms. Outcomes for patients who received an MP-guided versus MP-unguided therapy were compared. Progression-Free Survival (PFS) was the primary endpoint, while Overall Survival (OS) was the secondary endpoint. Patients' median age was 57 years, and female patients constituted 65% of the series. Thirty-one patients were newly diagnosed, and 69 patients had the MP performed upon disease recurrence or progression. Breast, lung, and colorectal cancers were the most frequent tumors. In 90 of the tested tumors, one or more aberrations were identified. In 61 patients, the MP results suggested at least one matched agent and guided therapy in 53 patients. Of all patients who received further therapy (83 patients), the median PFS was significantly longer in patients whose MP-guided versus those whose treatment was not guided (21.8 [95% CI; 14.5 - 29.1] vs. 10.9 [95% CI; 6.2 - 15.6] months, hazard ratio [HR] = 0.34 [95% CI; 0.17 - 0.69], P = 0.002). The benefit was largely shown in patients with recurrent or progressive disease (HR = 0.32 [95% CI; 0.14 - 1.20.75]; P = 0.006). While patients who received MP-guided therapy had numerically higher OS rates, that difference was not significant. This preliminary experience demonstrated MP's feasibility for cancer patients with a significant improvement in PFS, albeit a lack of OS benefit. Further research is warranted to address the inherent challenges for the universal adoption of MP in daily practice.

Abbreviations

MP: Molecular Profiling; OS: Overall Survival; PFS: Progression-Free Survival

Introduction

In the present era of precision medicine, recent advances in molecular cancer biology have led to the identification of tumor-specific molecular aberrations that could be exploited to inform tumor diagnosis, prognosis, and drive therapeutic decisions by precisely targeting such aberrations [1-3].

Currently, there is no uniformity concerning the clinical utility of comprehensive Molecular Profiling (MP) in patients with solid tumors, and the only randomized trial conducted so far showed no benefit of MP-guided targeted therapy. In that phase II SHIVA study, Le Tourneau et al. randomized 197 pretreated patients with solid tumors to receive a matched molecularly targeted agent or treatment at a physician's choice [4]. No Progression-Free Survival (PFS) difference was demonstrated; however, in a recent update, it was concluded that patients who crossed over from the control arm to the experimental arm achieved a 30% improvement in PFS [5].

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Another study, the My Pathway trial, evaluated the effectiveness of several targeted therapies in 35 tumor types (in 230 patients) that harbor genetic alterations not labeled for such treatments [6]. The study concluded that the approved targeted therapy regimens achieved responses in several refractory solid tumor types that were not labeled for these agents.

We recently reported our preliminary analysis of the MP of 50 consecutive adult patients with solid metastatic cancers refractory to standard of care [7]. The median PFS was improved among those whose therapy decision was guided by the MP findings (12.0 months) compared with those whose MP could not recommend a specific management decision (5.2 months). While there was no significant Overall Survival (OS) difference, the 12 month OS rate was 64% *vs.* 53%, respectively.

The current study aimed to provide a more mature analysis and a longer follow-up of prospective, comprehensive MP of tumors from a series of 100 consecutive patients with solid tumors using Next-Generation Sequencing (NGS). There has been no data about the use of tumor profiling among cancer patients in Saudi Arabia or the nearby countries to the best of our knowledge. Moreover, there are no local institutional or national guidelines that direct clinicians to exploit the emerging technology to achieve a better patient outcome.

Methods

Patients

Between May 2017 and April 2020, the first 100 consecutive adult patients with solid tumors whose tumors were tested for MP were included in the current analysis. Molecular profiling was requested for several patient groups: at diagnosis for those whose tumors are associated with benefit from known targetable agents; e.g., lung cancer, those whose initial diagnosis is linked to a poor prognosis, or patients presented with metastatic disease. MP was also performed for patients who demonstrated recurrence, progression, or refractoriness to the care standard. MP was only performed for patients with an acceptable performance status to permit further therapy (Eastern Cooperative Oncology Group performance status 0 to 2).

Molecular profiling methods

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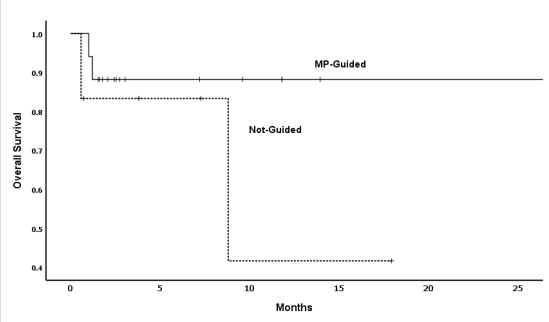

Figure 1: Progression-free survival (PFS) curves of molecular profiling-guided (solid line) and molecular profiling unguided (dashed line) patients.

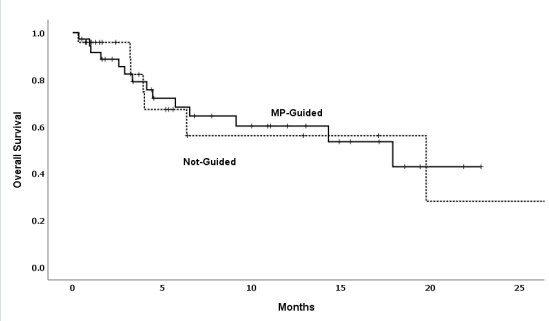

Figure 2: Overall survival (OS) curves of molecular profiling-guided (solid line) and molecular profiling-unguided (dashed line) patients.

MP was performed on archival fixed formalin paraffin-embedded tissue either from the primary tumor site or from a metastatic lesion if feasible using either of two commercially available NGS platforms, i.e., Foundation One (Foundation Medicine, Inc.) or OncoDEEP (OncoDNA, Inc). The NGS mutational analysis using the Foundation One was based on a panel of genetic mutations in 324 genes and two genomic signatures in any solid tumor [8]. In comparison, the OncoDEEP platform is based on NGS of 75 cancer-related genes, besides several immunohistochemistry tests, including protein phosphorylation to study protein expression [2].

Decision-making

The findings of the MP for each patient were discussed at a multidisciplinary molecular tumor board to recommend further management. A treatment was considered "matched" if there was an agent(s) that could target an aberration in a patient's MP or a functionally active protein expressed in the tumor and guide therapy decision. Upon obtaining the MP results, the treatment decision was either: 1) uphold the current treatment, or recommend changing/initiating a different treatment as guided by the MP results; or 2) uphold the current treatment, or recommend changing/starting another treatment not driven by the MP results. Implementing the first or the second recommendation was considered as either an MP-guided or MP-unguided decision, respectively.

Statistical methodology

PFS was defined as the interval between the date of implementing a management decision based on MP to the date of progression or death of any cause, whichever came first. OS was defined as the interval between the date of implementing a management decision based on MP to the date of death of any cause or date of the last follow-up. Survival functions were estimated using the Kaplan-Meier method, and survival between groups was compared using the log-rank test. All tests were two-sided at the 5% significance level. All statistical analyses were done with SPSS statistical package (IBM SPSS Statistics for Windows, version 25.0., New York, USA).

Results

The median age (95% CI) in years for the entire population was 57 (54 - 60) years, with males on average older (60 [53 - 67]) than females (56 [52 - 60]). Table 1 shows patients and disease characteristics. More females than males (65% v 35%), breast cancer, lung cancer, colorectal cancer, and pancreatic cancer were the most common primary tumor sites. In 31 patients, MP was performed at initial diagnosis, while in 69 heavily pretreated patients, it was done upon disease recurrence or progression.

The median interval (95% CI) between initial diagnosis and the MP was 10.2 (6.1 - 17.7) months. Table 2 depicts the summary results of the performed molecular testing. Almost a quarter of the tumors showed PD-L1 expression of >1%, and an Immunohistochemistry (IHC) positivity for CD 8, while microsatellite instability and tumor mutational burden of >10 megabases were uncommon, 2% and 3%, respectively. In 90% of the tested tumors, one or more aberrations were identified by NGS, while in 50 tumors were tested by IHC for protein expression, 41 showed one or more aberrations. Table 3 shows most of the identified aberrations with TP53, PIK3CA, and RAS mutations being the most frequently detected.

Table 4 depicts the entire population's management decision, newly diagnosed patients, and those with recurrent or progressive disease. In 61 patients, the MP results suggested at least one matched agent. MP guided therapy decision in 53 of those 61 patients (87%),

Table 1: Patient and disease characteristics.

Gender	No.
Female	65
Male	35
Diagnosis	
Breast	20
Lung	13
Colorectal	12
Pancreas	11
Ovary	8
Sarcoma	6
Endometrium	4
Unknown primary	4
Head and Neck	3
Other	19
Timing of molecular profiling testing	
At initial diagnosis	31
At disease recurrence or progression	69
Prior treatment	
Surgery	57
Chemotherapy (range 0 - 4 lines)	72
Endocrine therapy	18
Anti-CD 4/6	13
HER-2 targeted therapy	5

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Table 2: Results of the molecular profiling studies.

Method	No.
FoundationOne	50
OncoDeep	50
PD-L1	
≥ 1%	22
< 1%	53
Not done	25
Microsatellite	
Stable	94
Unstable	2
Not done	4
CD 8	
Positive	28
Negative	22
Not done	50
Alterations (NGS)	
Positive	90
Negative	10
Alterations (IHC)	
Positive	41
Negative	9
Not done	50
TMB	
More than 1 megabase	46
1 to 10 megabase	43
>10 megabase	3
Negative	49
Not done	5
Loss of homozygosity (8 ovarian cancer patients)	
Positive (14%, 24%, 29%)	3 (38%)
Negative	5 (62%)

17 of 31 newly diagnosed patients (55%), and 36 of 69 (52%) of those with recurrent or progressive disease.

Six of the newly diagnosed patients received no further therapy; of those, two patients with metastatic pancreatic cancer, and two with metastatic lung cancer were not fit for or declined systemic chemotherapy. None of those patients had potential matched therapy. Two patients with advanced ovarian cancer were not candidates for Poly (ADP-ribose) polymerase inhibitors maintenance as they had homologous recombination proficient with or without *BRCA* wild tumors. Of the 69 patients with recurrent or progressive disease, 11 patients were not given further therapy due to deterioration in performance status (8 patients) or loss to follow-up (3 patients). Eight of these 11 patients had potential matched treatment.

Progression-free survival

The database was looked on April 30, 2020, and the median follow-up from the date of MP testing was 16.0 (95% CI; 12.7 - 19.4) months. Five, 61, and 34 patients were alive with no evidence of disease, alive with disease, and dead, respectively.

All PFS dates were based on the computation of PFS from the date of MP testing. After excluding patients where no further therapy was offered, the median PFS was significantly longer in patients whose treatment with guided by MP versus those whose treatment was not guided (21.8 [95% CI; 14.5 - 29.1] *vs.* 10.9 [95% CI; 6.2 - 15.6] months, hazard ratio [HR] = 0.34 [95% CI; 0.17 - 0.69], $P = 0.002$) (Figure 1).

Among the newly diagnosed patients, implementing decisions based on MP results was not associated with PFS benefit. The median PFS in patients treated as guided by MP results as compared with that in patients whose treatment was not guided (not reached *vs.* 10.9 [95% CI; 1.0 - 20.8], with HR of 0.63 [95% CI; 0.12 - 3.3]; $P = 0.59$).

On the other hand, among patients with recurrent or progressive disease, there was a significant difference in median PFS between patients treated as guided by MP results as compared with that among patients whose treatment was not guided (21.8 [95% CI; 14.1 - 29.6] *vs.* 12.0 [95% CI; 4.4 - 19.6] months, HR = 0.32 [95% CI; 0.14 - 1.20.75]; $P = 0.006$).

Overall survival

OS dates were based on the computation of OS from the date of MP testing to the last follow-up or death from any cause. The median OS was 27.8 (95% CI; 21.4 - 34.3) months in the entire population. After excluding patients where no other therapy was given, there was a trend of an improved median OS among patients whose received MP-guided therapy versus those whose treatment was not guided (32.0 [95% CI; 25.5 - 38.5] *vs.* 25.0 [95% CI; 11.5 - 38.5] months, HR = 0.45 [95% CI; 0.20 - 1.03], $P = 0.052$) (Figure 2).

Among the newly diagnosed patients, the median OS has not been reached; however, the 12- and 24-month OS rate (± standard error) was 76% (8%) and 70% (9%), respectively. In this group, after excluding those who were not given any further treatment, there was no difference in the median OS between those who received MP-guided versus MP-unguided therapy (median OS was not reached vs. 8.8 [95% CI; 13 - 18.8 months], HR = 0.30 [95% CI; 0.04 - 2.2], $P =$

Table 3: Frequency of identified aberrations.

Aberration	No.
TP53/P53	47
PIK3CA	18
RAS/KRAS	17
APC	13
TOPO1/TOP2A	13
CDKN2A	11
FGFR1	10
TUBB3	9
MYC	8
PTEN	8
CCND1	7
ERBB2	7
TS	5
RB1	5
BRCA2	5
BRCA1	4
FGF	4
AKT	3
KDM5A	3
ESR1	4
CYP2D6	4
BRAF	2
EGFR	1
ALK	1
TRK	1
CHEK2	1
Others	86

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Table 4: Decision-making based on the results of the molecular profiling.

Management decision	No.
Guided by molecular profiling	53
Uphold current therapy	24
Change/initiate therapy	29
Not-guided by molecular profiling	30
Uphold current therapy	23
Change/initiate therapy	7
No further therapy	17
Management decision according to the timing of molecular profiling testing	
New diagnosis	31
Guided by molecular profiling	17
Not guided by molecular profiling	8
No treatment	6
Recurrent or progressive disease	69
Guided by molecular profiling	36
Not guided by molecular profiling	22
No treatment	11

Table 5: Overall survival rates.

	OS % (± standard error)			
	No treatment	**MP-Guided**	**MP-unguided**	**All**
Newly diagnosed disease				
6-month	45 (19)	87 (8)	42 (3)	83 (6)
12-month	-	87 (8)	-	76 (8)
24-month	-	-	-	70 (9)
Recurrent or progressive disease				
6-month	56 (2)	94 (4)	92 (6)	93 (3)
12-month	-	88 (6)	92 (6)	88 (4)
24-month	-	62 (9)	26 (2)	55 (8)

0.21).

Likewise, among patients with recurrent or progressive disease, there was no significant difference in median OS between the two groups (32.0 [95% CI; 16.9 - 47.1] *vs.* 25.0 [95% CI; 13.1 - 36.9], HR = 0.49 [95% CI; 0.20 - 1.2]; $P = 0.13$]).

Table 5 showed the OS probability rates of patients according to their status and if the MP results guided a management decision. Numerically, the OS rates for patients who received their treatment as MP-guided achieved higher survival rates as compared with those whose therapy was unguided. That advantage was shown in newly diagnosed patients and in patients with disease recurrence or progression.

Discussion

In 90% of our patients, at least one aberration was identified. The prevalence of detected aberration is influenced by the population examined, the method used, and the number of aberrations intended to be examined. Tsimberidou et al. using a polymerase chain reaction, detected at least one aberration in 40% of patients [9]; on the other hand, using the NGS method, Wheler et al. tested 339 patients and detected a potentially actionable target in 94% of patients [10].

In the current series, tumors in 61 patients identified potential matched agent(s), and in 53 patients (87%), the identified therapy was used. The rate of implementing matched therapy in our series was relatively higher than those reported from other studies [10,11].

Applying the MP guidance achieved a PFS advantage with a 66% reduction in the risk of progression or death (HR = 0.34). The demonstrated benefit was almost identical to that shown in our earlier series [7]. The advantage was evident, particularly in patients with recurrent or progressive disease. On the other hand, no significant OS difference was shown between the MP-guided and the unguided groups.

Nevertheless, as shown in Table 5, the OS rates were numerically higher among those whose treatment decision was MP-guided. The increased OS rates were observed in newly diagnosed patients and among those with disease recurrence or progression. Some several plausible reasons and limitations may explain the lack of OS advantage. First, we only analyzed a small sample of 100 patients, which may have precluded the demonstration of OS advantage. Second, this series included a diverse patient population of different tumor types, besides the inclusion of newly diagnosed patients and patients with disease recurrence or progression. Third, in 39 patients, no targetable aberration was identified. Lastly, intervention post-progression was not controlled and was implemented according to the individual physician's choice. Despite those limitations, our series represents the only available data concerning prospective MP from Saudi Arabia and perhaps from the entire Middle East region to the best of our knowledge.

It is prudent to acknowledge that larger series have also reported conflicting evidence. In a nonrandomized phase I trial, conducted by the MD Anderson Cancer Center and included 1,144 patients with advanced cancer, it was found that patients with one aberration who

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received matched therapy demonstrated higher objective response and superior survival compared with that among those treated with non-matched drugs. However, the advantage was not shown when 2 or 3 molecular alterations were present [11].

The PREDICT-trial enrolled 347 patients with advanced solid tumors, and a quarter of patients were treated according to their genomic profile [12]. Improvement in PFS was demonstrated in patients treated with a matched therapy compared with the control group; however, no improvement in OS was observed.

One of the most compelling evidence was reported by Schwaederle et al. [13]. The authors conducted a meta-analysis of 570 phase II single-agent studies, mainly nonrandomized (> 80% of the studies), and incorporating 32,149 patients. The meta-analysis concluded that using a personalized strategy was associated with a higher response rate and longer PFS and OS as compared with the non-personalized approach.

Despite the quantum leap progress in our understanding of tumor biology and the resulting evolution of MP, several challenges face the wider use of MP in the daily practice. While MP's results may identify a targetable aberration, the known tumor heterogeneity could certainly influence the clinical outcome [14]. Additionally, there are several other challenges: the uncertainty surrounding whether the complex MP report influences the oncologist's treatment decisions, lack of confidence of physicians in genomic knowledge and how they could interpret MP reports, uncertainty related to the clinical utility of the information, and undoubtedly the associated economic burden [15-17].

Conclusion

Although there have been clear successes in the era of molecular characterization, MP's clinical utility remains unproven. Precision medicine among cancer patients remains a major challenge for the oncology community but could enhance more therapeutic options to be exploited. Future research should be able to address the most efficient and validated platform, the most reliable biomarkers that help to select appropriate patients, the most reliable fluid biopsy technique [18], and ways to lower the inherent cost to make MP affordable, particularly for patients in developing and low-income countries [19].

References

1. Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL (2020) Molecular profiling for precision cancer therapies. Genome Med 12: 8.
2. Laes JF, Aftimos P, Barthelemy P, Bellmunt J, Berchem G, et al. (2018) The clinical impact of using complex molecular profiling strategies in routine oncology practice. Oncotarget 9: 20282-20293.
3. Zimmer K, Kocher F, Spizzo G, Salem M, Gastl G, et al. (2019) Treatment according to molecular profiling in relapsed/refractory cancer patients: a review focusing on latest profiling studies. Comput Struct Biotechnol J 17: 447-453.
4. Le Tourneau C, Delord JP, Goncalves A, Gavoille C, Dubot C, et al. (2015) Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 16: 1324-1334.
5. Belin L, Kamal M, Mauborgne C, Plancher C, Mulot F, et al. (2017) Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer: cross-over analysis from the SHIVA trial. Ann Oncol 28: 590-596.
6. hainsworth jd, meric-bernstam f, swanton c, hurwitz h, spigel dr, et al. (2018) targeted therapy for advanced solid tumors on the basis of molecular profiles: results from mypathway, an open-label, phase IIa multiple basket study. J Clin Oncol 36: 536-542.
7. Ibrahim E, Eldahna WM, Refae A, Bayer A, Mansoor I, et al. (2019) Genomic profiling for patients with solid tumors: a single-institution experience. Annals of Clinical Oncology 2: 1-7.
8. https://www.foundationmedicine.com/genomic-testing/foundation-act. FMGTF.
9. Tsimberidou AM, Iskander NG, Hong DS, Wheler JJ, Falchook GS, et al. (2012) Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. Clin Cancer Res 18: 6373-6383.
10. Wheler JJ, Janku F, Naing A, Li Y, Stephen B, et al. (2016) Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. Cancer Res 76: 3690-3701.
11. Tsimberidou AM, Wen S, Hong DS, Wheler JJ, Falchook GS, et al. (2014) Personalized medicine for patients with advanced cancer in the phase I program at MD Anderson: validation and landmark analyses. Clin Cancer Res 20: 4827-4836.
12. Schwaederle M, Parker BA, Schwab RB, Daniels GA, Piccioni DA, et al. (2016) Precision Oncology: The UC San Diego Moores Cancer Center PREDICT Experience. Mol Cancer Ther 15: 743-752.
13. Schwaederle M, Zhao M, Lee JJ, Eggermont AM, Schilsky RL, et al. (2015) Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. J Clin Oncol 33: 3817-3825.
14. Le Tourneau C, Kamal M, Tsimberidou AM, Bedard P, Pierron G, et al. (2016) Treatment Algorithms Based on Tumor Molecular Profiling: The Essence of Precision Medicine Trials. J Natl Cancer Inst 108: djv362.
15. Gray SW, Hicks-Courant K, Cronin A, Rollins BJ, Weeks JC (2014) Physicians' attitudes about multiplex tumor genomic testing. J Clin Oncol 32: 1317-1323.
16. Horgan D, Jansen M, Leyens L, Lal JA, Sudbrak R, et al. (2014) An index of barriers for the implementation of personalised medicine and pharmacogenomics in Europe. Public Health Genomics 17: 287-298.
17. Meric-Bernstam F, Brusco L, Shaw K, Horombe C, Kopetz S, et al. (2015) Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials. J Clin Oncol 33: 2753-2762.
18. Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, et al. (2018) Circulating Tumor DNA Analysis in Patients with Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol 36: 1631-1641.
19. Nelson B (2014) Genomic medicine: a question of value: despite the promise of personalized medicine, genomic testing has yet to prove its cost-effectiveness. Cancer Cytopathol 122: 557-558.