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Molecular Tumor Boards: Realizing Precision Oncology Therapy

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Abstract

Technological advances in high-throughput next-generation sequencing (NGS) along with advances in computational processes have brought about the dawn of the genomic medicine era. NGS has enabled molecular characterization of malignancies, and facilitated the development and approval of gene- and immune-targeted therapies, both of which impact the mutanome. Clinical implementation of this technology, approval of novel targeted agents, and establishment of molecular tumor boards has enabled precision oncology to become a reality.

CURRENT STATUS AND PROGRESS

Molecular tumor boards (MTBs) are the logical evolution of the traditional tumor boards in the era of genomic medicine, and, as such, are now emerging at large academic medical centers. MTB meetings provide an avenue for clinicians to gain an understanding of how a patient's tumor genomics may help guide treatment decisions and consequently actualize precision oncology.

It has been about 4 years since the inception of the MTB at the University of California, San Diego (UCSD) Moores Cancer Center.^{1,2} The defining characteristic of an MTB is the interdisciplinary team consisting of not only medical and radiation oncologists, radiologists, pathologists, and surgeons, but also including geneticists, bioinformatics specialists, basic/translational scientists, immunology experts, and, at UCSD, faculty from the Supercomputer Center who conduct *in silico* modeling to simulate the impact of genomic alterations on the affected protein(s) structure and function. These meetings cut across disease types and include experts in various cancer histologies. The objectives of the MTB are analogous to that of a regular tumor board—discuss patients with difficult-to-treat cancers and help the

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AUTHOR CONTRIBUTIONS

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Additional Supporting Information may be found in the online version of this article.

CONFLICT OF INTEREST/DISCLOSURE

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treating physician to make the best decision for their patient. However, the MTB is unique in that the treatment recommendations are not just based on patient's classical history, pathology, and imaging, but also incorporate a thorough review of the patient's clinical-grade tumor genomics (and, in some cases, transcriptomic and proteomic) information. The goal is to match patients with the right drug or combination of drugs based on their biomarker portfolio. Patients may be guided to therapy with genomically targeted agents, radiotherapy, cytotoxic chemotherapy, hormone modulators, and immunotherapies, or combinations of the above, based on the classic characteristics of their tumor and of the tumor molecular profile.

The specific composition of the MTB at UCSD, the meeting organization, and the genomic tests that are routinely ordered have previously been detailed.^{1,2} Overview of the workflow for tumor genetic profiling and MTB case evaluation is depicted in Figure 1a,b. The essential characteristics that have enabled the implementation of the MTB recommendations into clinical practice at UCSD are discussed here (Table 1).

EXISTING HURDLES AND POTENTIAL SOLUTIONS

One of the earlier barriers to clinical implementation of precision oncology was the availability of gene panels covering only a limited number of cancer-related genes and the turnaround time in obtaining the genomic results. Since implementing our MTB, commercially available clinical laboratory improvement amendment (CLIA) certified gene panels have increased the number of genes interrogated to several hundred genes. UCSD has also developed its own NGS panel of 397 genes. The rapid advancement of NGS technology together with a precipitous fall in costs, as well as identification and validation of additional driver oncogenes genes, have resulted in an increase in the number of genes covered by these clinical-grade panels.¹⁻³ In our experience with the use of a 182- or 236-gene panel, a median of four molecular aberrations (range, 1–14 aberrations) were identified per patient, and >90% of these patients had a theoretically actionable alteration.^{1,2} Overall, 25–35% of patients then can receive genomically guided therapy in our and other's experience,¹⁻⁴ a rate that is higher than in some other studies, perhaps because of the use of smaller, hot-spot panels in those reports. One of the most common barriers to implementing MTB recommendations into clinical practice has been patient disease progression/deterioration prior to therapy implementation, suggesting that genomic profiling should be performed earlier in the disease course.⁴ At UCSD, treating physicians have adjusted their practice and often order genomic tests prior to patient's tumor progression so that the results will be available when needed. Turnaround time for receipt of results has decreased and is about 4 weeks, with 2 of those weeks being the time taken to acquire a new tissue biopsy or to get the release of archived tissue from the pathology laboratory. The recent availability of noninvasive tumor sequencing tests utilizing patient's blood to identify circulating tumor DNA (ctDNA) has made it possible to further reduce the time from ordering to results, and to perform serial tests to monitor dynamic changes in molecular profiles. Other barriers to the utilization of genomics to inform therapy selection include access to appropriately targeted clinical trials, insurance coverage for off-label drug use, and patient or physician preference.^{1,2,4}

At the UCSD Center for Personalized Cancer Therapy, implementation of MTB recommendations for genomically matched therapy for a patient is completed with a precision oncology protocol in place, which allows patients to be educated via consent regarding the genomically guided treatment. The UCSD PREDICT (Profile Related Evidence Determining Individualized Cancer Therapy–NCT02478931) protocol has been reviewed and approved per Institutional Review Board guidelines. This protocol permits a streamlined process for enrolling and obtaining patient consent and enables review of treatment outcomes that helps fuel reverse translational research. Several other protocols are also in place. The idea is to have master or umbrella studies that embrace the majority if not all potential patients.

Other hurdles in implementing MTB suggestions include the lack of accessibility or patient ineligibility for clinical trials.^{1,2,4} These hurdles can be remedied by maintaining a robust clinical trial portfolio along with employing dedicated patient navigators to help find the right clinical trial for the patient in order to improve patient accessibility and patient awareness of genomically or immunologically targeted agents (Table 1). Furthermore, increasing patient access to clinical trials by expanding clinical trial eligibility and through development of novel, genomically informed clinical trial designs are also needed. Additionally, at UCSD, we have employed a medication acquisition specialist to help patients obtain coverage for off-label use of gene- and immune-targeted agents.

FUTURE THOUGHTS FOR IMPROVEMENT

The MTB is also a vehicle by which precision immuno-oncology can be realized. One of the key challenges in the field of cancer immunotherapy is the identification of patients who would respond best to any given immunotherapy and the possible dependence of this response to the unique mutational landscape of the patient's tumor. The use of genomic tests along with other biomarkers, such as PD-1/PD-L1 quantitation by immunohistochemistry, can better guide patient selection for treatment with currently approved immunotherapy or recommendations for immunotherapy clinical trials. It is becoming increasingly apparent that patient tumor genomics can impact selection of immunotherapy as the therapeutic option. This is best exemplified by recent accelerated approval of pembrolizumab for patients with tumors harboring DNA mismatch repair deficiency (dMMR) displaying high levels of microsatellite instability (MSI-H) irrespective of tumor histology. It is currently understood that patients with dMMR develop MSI-H tumors characterized by higher tumor mutational burden. The increase in the absolute number of insertion, deletion, and nonsynonymous mutations increases the probability of expression and presentation of specific immunogenic neo-antigens by tumor cells, which may be recognized by the host immune system, leading to an antitumor immune response.

In addition to identifying predictive markers of response, there is also a growing body of evidence that supports the notion that genomic profiling can help identify predictive markers of resistance to immunotherapy (e.g., functional loss of *JAK1/JAK2* or *MDM2* amplification, with the latter correlating with accelerated progression (designated hyperprogression)). The search for predictive biomarkers of response and resistance to immunotherapy is in its nascent stage, and will undoubtedly lead to incorporation of

additional complex diagnostics such as microbiome sequencing and whole exome sequencing (WES) coupled with transcriptome sequencing. The data generated from these advance platforms will require significant computational and biological expertise to distill the data and convey the results to the treating clinicians, which would be best accomplished by the interdisciplinary team that constitutes an MTB. Additionally, the systematic integration of the molecular biomarker and clinical data will support reverse translational studies to identify novel mechanisms of resistance and potentially novel therapeutic targets. This is exemplified in a report by Beltran *et al.*,⁵ which demonstrated that WES along with transcriptomic analysis can be implemented into clinical workflow. The analysis enabled complete characterization of an exceptional responder, and inspired translational research that led to identification of a genomic alteration observed in subsets of ovarian and prostate cancer, which may make them particularly sensitive to treatment with platinum-based chemotherapy.⁵

CONCLUSION

The implementation of the MTB at UCSD and at other larger academic institutions has enabled the practice of precision oncology. The treatment outcomes from our observational single-center PREDICT study are similar to other reports that support the implementation of genomic profiling and MTB to select genomically and immunologically guided therapies for patients with actionable genomic aberration(s).^{1–4} However, the benefit of precision cancer medicine still needs additional confirmation in larger prospective clinical trials utilizing genomic profiling. Genomically guided large prospective clinical trials such as NCI-MATCH (NCT02465060), LUNG-MAP (NCT02154490), and TAPUR (NCT02693535) will ultimately help answer some of the fundamental questions in precision oncology. The results from these trials will enable advances in the implementation of precision oncology, which, in clinical practice, is facilitated through an MTB with expert members.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Overview of molecular tumor board case evaluation. Abbreviations: molecular tumor board (MTB), immunohistochemistry (IHC), fluorescence in situ hybridization (FISH). *Genomic aberration defined as base substitution, rearrangement, insertion, deletion, or amplification. Additionally, vendors may also report detection of select cancer biomarkers such as microsatellite status and tumor mutation burden. (b) Case presentation. Case: 30-year-old woman with periosteal osteosarcoma of left femur with lung metastases presented after progressing on cytotoxic chemotherapies including doxorubicin, cisplatin, and high-dose ifosfamide. Genomic analysis of tumor tissue with 315-gene panel revealed multiple alterations including *MDM2*, *CDK4*, *CCND2*, *FRS2*, and *FGF6/23* amplifications. The case was presented at the molecular tumor board. MTB Recommendation: Based on the alterations, lenvatinib 10 mg PO daily (a multi-tyrosine kinase inhibitor including FGFR) (targeting *FRS2* and *FGF6/23* amplifications) plus palbociclib 75 mg PO daily: 3 weeks on, 1 week off (CDK4/6 inhibitor targeting *CDK4* and *CCND2* amplifications) were discussed.

Patient was consented for PREDICT (Profile Related Evidence Determining Individualized Cancer Therapy) protocol (NCT02478931) and started on the recommended combination. Treatment Outcomes: Two months after start of therapy, FDG-PET scan showed interval improvement in the hypermetabolic mass at the right lung (b: left and middle). At 4 months, patient continued to experience metabolic response and tumor regression with partial response documented (b: right). Patient is progression-free 6+ months as of June 2017. Overall, the combination therapy is tolerable, with the patient experiencing Grade 1 diarrhea and Grade 1 abdominal pain (grading according to Common Terminology Criteria for Adverse Events, v. 4.03).

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Table 1

Molecular tumor board: essential characteristics, challenges, and solutions

Essential characteristics	Leadership knowledgeable in clinical care and genomics	
	Attendees to include pathologists, radiologists, surgeons, medical oncologists, cell signaling scientists, bioinformatics specialists, geneticist	
	Manager to coordinate handouts, continuing education credits, and to provide other operational support	
	Dedicated radiologist to review films	
	Dedicated pathologist to review pathology	
	Clinical trials navigator for helping to enroll patients into appropriate clinical trials	
	Umbrella protocol on which patients can be treated	
Challenges	Solutions	
Drug access	•	Medication acquisition specialist to help patients obtain coverage or assistance needed to access required medication
	•	Clinical trial navigators knowledgeable in clinical trials available locally and elsewhere
	•	Large clinical trial portfolio of genomically targeted agents and immunotherapeutics
Ordering genomic tests	•	Coordinator to assist with logistics of ordering genomic and other biomarker orders
Clinical trial availability	•	Umbrella, master protocol on which to treat patients
	•	Coordinator to help consent patients