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Molecular Tumor Board: The University of California San Diego Moores Cancer Center Experience

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Abstract

Objective. DNA sequencing tests are enabling physicians to interrogate the molecular profiles of patients' tumors, but most oncologists have not been trained in advanced genomics. We initiated a molecular tumor board to provide expert multidisciplinary input for these patients.

Materials and Methods. A team that included clinicians, basic scientists, geneticists, and bioinformatics/pathway scientists with expertise in various cancer types attended. Molecular tests were performed in a Clinical Laboratory Improvement Amendments environment.

Results. Patients ($n = 34$, since December 2012) had received a median of three prior therapies. The median time from physician order to receipt of molecular diagnostic test results was 27 days (range: 14–77 days). Patients had a median of 4 molecular abnormalities (range: 1–14 abnormalities) found by next-generation sequencing (182- or 236-gene panels). Seventy-four genes were involved, with 123 distinct abnormalities. Importantly, no two patients had the same aberrations, and 107 distinct abnormalities were seen only once. Among the 11 evaluable patients whose treatment had been informed by molecular diagnostics, 3 achieved partial responses (progression-free survival of 3.4 months, ≥6.5 months, and 7.6 months). The most common reasons for being unable to act on the molecular diagnostic results were that patients were ineligible for or could not travel to an appropriately targeted clinical trial and/or that insurance would not cover the cognate agents.

Conclusion. Genomic sequencing is revealing complex molecular profiles that differ by patient. Multidisciplinary molecular tumor boards may help optimize management. Barriers to personalized therapy include access to appropriately targeted drugs. ***The Oncologist*** 2014;19:631–636

Implications for Practice: Our study relates our experience with the initiation of molecular tumor board meetings, which are a new vehicle for managing patients with complex malignancies on whom molecular diagnostics have been performed. This experience could be of significant importance to oncologists who are increasingly faced with advanced molecular diagnostic data, yet have minimal training in genomics. Our article should help clinicians to handle practical issues related to setting up and efficiently utilizing molecular tumor board meetings. We also aim at helping oncologists and health care systems understand and address practical, logistical, and scientific issues, such as the challenges associated with interpretation of molecular testing for patients with advanced cancer.

Introduction

Technological developments in genomic sequencing are advancing at a breathtaking rate. These tests are rapidly being made available in the clinic, potentially facilitating a personalized treatment strategy [1–4]. The collaboration between biologists who interpret and confirm the functional relevance of molecular abnormalities and clinicians who assess relationships to cancer prognosis and response to therapy has led to the discovery of the activity of molecularly targeted drugs. These advances have greatly increased our understanding of the molecular basis of tumor progression and treatment response. From the experience with the HER2 antibody trastuzumab in breast cancer [5–7], to experiences with the Bcr-Abl inhibitor imatinib in chronic myelogenous leukemia [8–11] and the epidermal growth factor receptor (EGFR)

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inhibitors gefitinib and erlotinib in non-small cell lung cancer [12–16], through the recent experience with the BRAF inhibitors vemurafenib and dabrafenib in melanoma [17–19] and the dual Alk/Met inhibitor crizotinib in ALK-rearranged non-small cell lung cancer [20–22], the success of combining molecular diagnostics and targeted treatments has been well-documented [23–29]. Although some molecular aberrations predict for response to cognate inhibitors, others can foretell resistance; for example, *KRAS* mutations in colorectal cancer are associated with resistance to the EGFR antibody cetuximab [30]. As robust but complex genomic sequencing technology has become available, there is a need for oncologists to have access to experts in fundamental molecular biology to effectively translate tumor genotype into personalized patient care.

Oncology tumor boards are a long-standing tradition in medicine. They are typically held as disease group meetings that occur on a regular basis and bring together medical oncologists, surgeons, radiation therapists, pathologists, and radiologists with expertise in a histologic type of cancer. Patients whose problems are difficult are usually presented, the films and pathology are reviewed, and a consensus opinion regarding treatment is rendered.

With the advent of molecular diagnostics, we initiated a molecular tumor board in December 2012. The molecular tumor board meetings were held every 2 weeks and emulated disease-specific tumor boards, as described above, but with a few key differences. First, because molecular abnormalities do not segregate by histology [31], experts in various cancer diagnoses were present. Second, we invited scientists with in-depth knowledge of a variety of cancer-related pathways to participate. Our overall goal was to gather a multidisciplinary team of experts in their fields comprising medical, surgical, and radiation therapy oncologists; biostatisticians; radiologists; pathologists with experience in molecular genetics and diagnostics; clinical geneticists; basic and translational science researchers; and bioinformatics and pathway analysis specialists to discuss patient cases for which molecular diagnostics had been performed. In this paper, we describe our early experience with the molecular tumor board at the University of California San Diego Moores Cancer Center.

Materials and Methods

Molecular Tumor Board Meetings and Organization

The molecular tumor board meetings were held for 1 hour every 2 weeks. All information was deidentified in compliance with Health Insurance Portability and Accountability Act privacy regulations. The molecular tumor board meeting was accredited for continuing medical education for physicians by the University of California San Diego School of Medicine.

The meeting was moderated by a senior physician experienced in clinical trials research, genomics data relevant to patients, and medical oncology. Two comoderators included a senior, highly-experienced medical oncologist and a midlevel oncologist who oversaw the cancer center biorepository. A handout prepared by the coordinator included a meeting agenda, deidentified patient information (age and sex, physician's name, diagnosis and date of diagnosis, last treatment and date of last treatment, biopsy site and date, molecular test used, molecular profile results, and room for comments about the discussion), and a copy of the key parts of the molecular diagnostic report. For this analysis, electronic medical records were reviewed for patients' characteristics and outcome. All patients included in this report signed an informed consent approved by the University of California San Diego institutional review board. Patients consented for analysis of their data as well as any investigational procedures or drugs.

The patient's doctor or a designated representative (e.g., nurse practitioner, physician assistant, fellow) presented the patient's case, giving a concise medical history including date of diagnosis, type of tumor, relevant markers, prior treatment history with response, and comorbidities. This was followed by projection of radiological images or scans and pathology (light microscopy), which were discussed by a radiologist and a pathologist, respectively. The results of the molecular profiling were then presented by the patient's physician or designee.

Attendees included representatives of medical oncology, surgery, and radiation therapy with expertise in diverse cancers; radiologists; clinical geneticists; and pathologists with experience in both histologic and molecular diagnostics. Basic and translational scientists and specialists in bioinformatics and pathway analysis also attended. The latter groups provided input based on their in-depth knowledge of relevant molecular pathways. Common discussion points included whether the aberrations were activating; the impact of several aberrations on various signaling pathways; whether germline aberrations might also be present in young patients who had mutations such as *TP53*, *RET*, and *ATM*; and which drugs, either approved or in clinical trials, might modulate the effect of the molecular aberrations. A consensus was reached as to a choice of agents that might be most usefully tailored to the patient's problem. The discussion of the board was considered advisory, with the choice of therapy ultimately decided by the "treating" physicians.

Molecular Testing

The most common tests (all Clinical Laboratory Improvement Amendments [CLIA]) were used. FoundationOne (Foundation Medicine, Cambridge, MA, http://www.foundationone.com) is a clinical-grade next-generation sequencing test that sequences the entire coding sequence of 182 cancer-related genes and 37 introns from 14 genes often rearranged in cancer and, more recently, 236 cancer-related genes and 47 introns from 19 genes often rearranged in cancer. ResponseDx (Response Genetics, Los Angeles, CA, https://p.responsedx.com) analyzes a panel of relevant gene aberrations, usually two to five (e.g., *EGFR, KRAS, EML4-ALK, HER-2/neu*), and expression of certain proteins (e.g., ERCC1, EGFR, TS, RRM1, MET, PIK3CA, HER-2/neu, depending on the disease) by disease type (lung, colon, gastric cancer, and melanoma panels). Molecular Intelligence (Caris Life Sciences, Phoenix, AZ, http://www.carismolecularintelligence.com/targeting_cancer) utilizes multiple technologies, such as immunohistochemistry, fluorescent in situ hybridization/chromogenic in situ hybridization, polymerase chain reaction, and next-generation sequencing. Champions Oncology (London, U.K., http://www.championsoncology.com) provides full-exome sequencing.

Results

Molecular tumor board attendance ranged from 25 to 40 people, with medical oncologists making up about 48% of attendance, joined by other physicians and practitioners including medical geneticists (14%), basic and translational scientists including pathway analysis specialists (14%), pathologists (10%), fellows and postdoctoral and other trainees (5%), and other staff (9%). At the time of data cutoff, 34 consented patients had been presented at 14 molecular tumor boards. A total of 10 different oncologists presented their patients.

Patient Characteristics

Among the 34 patients presented, the majority had breast cancer (16 of 34 [47%], three different oncologists), followed by gastrointestinal cancers (8 of 34 [23%], three different oncologist), head and neck cancers (4 of 34 [12%], one oncologist), lung cancers (2 of 34 [6%], one oncologist), and other types of cancers (epithelioid sarcoma, myoepithelial carcinoma, paraganglioma, and tumor of unclear origin; 4 of 34 [12%], two oncologists) (Fig. 1A, 1B). Median age of the patients presented was 56 years (range: 29–75 years), with 27 (79%) being women. Patients had received a median of three prior therapies in the metastatic setting (range: 1–13 therapies). At the time of molecular tumor board meeting presentation, 20 patients (59%) were on treatment; their physicians ordered molecular diagnostics in anticipation of possible future progression. The other patients had progressed on prior therapy, and their physicians presented their cases to receive expert input for their treatment or to validate therapy decisions made or possible future management decisions.

Molecular Diagnostic Tests: Process

Of the 34 patients presented, 33 had testing by FoundationOne next-generation sequencing (10 with the 182-gene panel and 23 with the 236-gene panel), 2 had testing by ResponseDx, 3 had testing by Molecular Intelligence, and 1 had testing by Champions Oncology (4 patients had testing done by more than one source). It took a median of 11 days for the tissue specimen to be acquired or, in the case of archived specimens, to be found and to reach the laboratory for the molecular testing (range: 1–58 days), and it took a median of 17 days to produce the results (range: 8–64 days). The median total time from physician order to receipt of molecular diagnostic test results was 27 days (range: 14–77 days). A range of billing mechanisms were applicable, reflecting the variety of test platforms; although insurance billing directly by the vendor was the most common mechanism, direct-to-patient billing was also seen.

Tests could be performed on fresh biopsies as well as on archived tissue. The median time of specimen acquisition (biopsy or surgery) was 3 months (range: 0–45.4 months) before ordering molecular diagnostics. The origin of the pathologic specimen sent for molecular diagnostic testing was from a metastatic site for 14 cases and from the primary tumor for 20 cases.

Molecular Diagnostic Tests: Results

There was a median of 4 molecular aberrations per patient (range: 1–14 aberrations) (Fig. 2A). An aberration was defined as a mutation, rearrangement, deletion, amplification, or

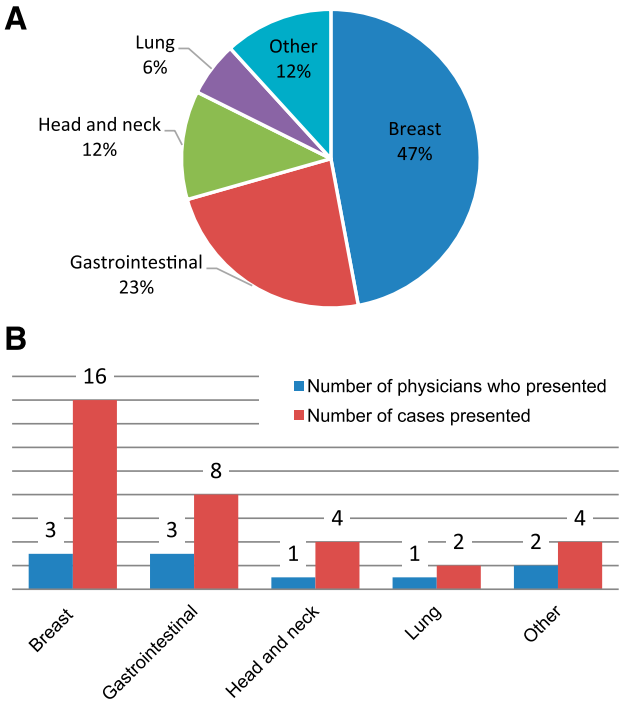

Figure 1. Patient characteristics. **(A):** Repartition of the cases presented at the molecular tumor board meetings by disease type. **(B):** Bar graph representing the number of cases presented by disease type (red bars) and by number of different attending physicians (blue bars).

insertion. All patients had at least one aberration. The highest number of aberrations seen in a single patient was 14 (diagnosis of breast cancer; assessed by next-generation sequencing of 236 genes by FoundationOne). Of interest, this patient had had tissue from the same metastatic site analyzed previously by the Ion AmpliSeq test (analyzes hotspot regions in 50 genes by multiplex polymerase chain reaction), and no abnormalities were found. Thirteen of the 14 abnormal genes detected by next-generation sequencing were not in the Ion AmpliSeq panel, and the 14th gene was in the panel but it was amplified (the Ion AmpliSeq hotspot panel detects point mutations but not amplifications).

Of interest, there were no two patients who had identical aberrations. A total of 74 genes were involved, with 123 distinct aberrations (if an aberration involved amplification vs. deletion vs. rearrangement vs. mutation in the same gene, it was considered distinct; in addition, if a mutation occurred in the same gene but involved distinct nucleotides in different patients, each was also regarded as distinct). The genes with the highest rates of abnormality were *TP53* (mutation; 17 of 33 patients, 51.5%); *MYC* (amplification; 10 of 33 patients, 30.3%); *PIK3CA* (mutation and, less commonly, amplification; 6 of 33 patients, 18.2%); and *KRAS* (mutation), *PTEN* (loss or mutation), *CDKN2A* (loss or truncation), *ERBB2* (amplification), and *APC* (mutation) (5 of 33 patients each, 15.2%) (Fig. 2B).

Patient Follow-Up and Outcome

Typically, the molecular test was ordered after several treatment failures. Once the results were received, there were two main case scenarios. Some physicians presented patients at the molecular tumor board while they were still on their prior

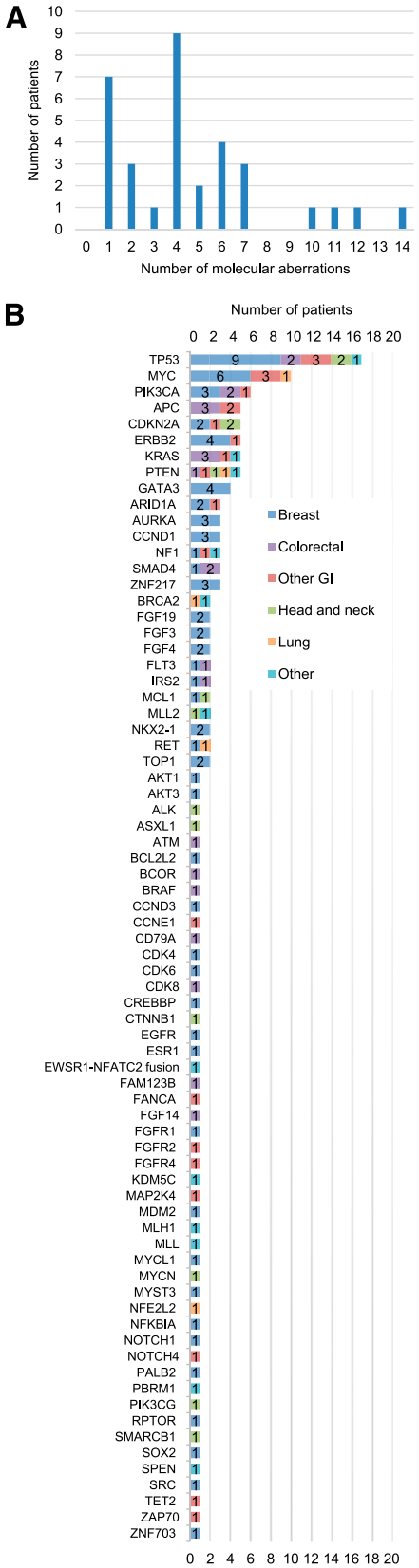

Figure 2. Molecular aberrations. **(A):** Number of patients by number of molecular aberrations. **(B):** Bar graph representing the number of patients with each specific gene aberration. For panels **(A)** and **(B)**, data on the 33 patients tested with the FoundationOne test were used (182- or 236-gene panel, next-generation sequencing).

Abbreviation: GI, gastrointestinal.

therapy (before progression) so that an alternative plan could be prepared for implementation at the time of therapy failure; others presented patients after their treatment failed. Of the 20 patients who were presented while still responding to their previous treatment, 7 showed subsequent disease progression and 4 of these initiated treatment based on molecular tumor board discussions. For 14 other patients presented, the previous treatment had already failed; 8 of these 14 patients were discussed at molecular tumor boards and initiated treatment.

The median time between molecular diagnostic results being received and the molecular tumor board patient presentation was 24 days (range: 2–144 days). To date, treatment decisions have been made according to the molecular results for 12 of 34 presented patients at a median of 1.5 months (range: 1.0–5.7 months) from physician order of molecular tests to start of therapy informed by the test. In the other 22 patients, molecular diagnostics did not inform treatment decisions for the following reasons: patients were stable on their previous treatment ($n = 13$); another treatment decision was preferred (because of lack of coverage for the cost of molecularly matched therapy or because the patient was not eligible for the clinical trial discussed and/or could not travel to the center conducting the trial; $n = 7$); aberrations were present but not actionable ($n = 1$); and one patient died close to the molecular tumor board meeting date.

Of the 12 patients treated so far on the basis of their molecular diagnostic results, 11 were evaluable (1 is too early). Three of those 11 patients achieved a partial response (progression-free survival [PFS] of 3.4 months, ≥6.5 months, and 7.6 months; four, three, and four prior therapies, respectively); one had a diagnosis of tumor of unclear origin, and two had a diagnosis of breast cancer. Four of those 11 patients had stable disease (for ≥2 months, ≥3 months, ≥3 months, and 4 months), and another 4 had progressive disease (PFS of 1 month, 2 months, <1 month, and <1 month).

Discussion

Because the price of powerful next-generation sequencing technologies has dropped precipitously (from about $3 billion in the year 2000 to approximately $5,000 or less today) [32, 33] and the accuracy and speed with which results can be obtained has increased quickly, genomic sequencing as a diagnostic tool is gaining widespread use in medical oncology. Furthermore, there is abundant evidence that many of the molecular abnormalities that are discerned drive the progression of cancer. With the rapid introduction of potent targeted agents into the clinic, molecular aberrations have also become druggable. However, most experienced physicians treating patients with cancer have not been trained in molecular biology, and the interpretation of these complex diagnostics requires multidisciplinary input that includes basic scientists and bioinformatics and pathway specialists. Furthermore, many of the patients on whom these diagnostics have been performed have exhausted several conventional therapies; therefore, a common approach to their management would include presentation at a tumor board to gain a consensus opinion for their next treatment.

Molecular tumor board meetings are a new vehicle for managing patients with complex malignancies on whom molecular diagnostics have been performed. The molecular tumor board meetings were distinct from classic tumor boards in that

they included physicians with expertise in a variety of different histologies (e.g., patients with seven different types of cancer have been presented to date), and the attendance of basic scientists and bioinformatics and pathway analysts was crucial so that the therapeutic suggestions could be optimally informed by the results of molecular interrogation of the patients' tumors. Clinical geneticists also attended because in some cases, especially in young patients, aberrations in the tumor might in fact be of germline origin (e.g., *TP53, RET, ATM*), with implications for both patients and their relatives. We found that there were several advantages to a molecular tumor board. In particular, group consensus, education of the treating physician (and other attendees), and improved efficiency (plans for new processes) in tumor tissue acquisition and testing emerged from these meetings. In addition, because many oncologists remain untrained in genomics, providing expert opinion to them increased their confidence in utilizing molecular diagnostics. Even so, the immense complexity of tumors and their genomic aberrations and the realization that, for instance, different mutations within the same gene can have distinct impacts suggest that increasingly sophisticated computer technologies will be crucial for optimal interpretation of the results. Moreover, resources should be invested in education, reporting, and improving access to trials when it comes to molecular testing.

We noted several limitations that are relevant to the current use of molecular diagnostics performed in a CLIA environment. First, the time to obtain results is still lengthy in the context of patients with advanced cancer, for whom treatment decisions are urgent. Indeed, it took a median of 27 days from the time the tests were ordered until results were available (although 10 days were spent obtaining fresh tissue or finding the appropriate archived specimens). Consequently, physicians started ordering tests before patients had failed current therapy. As molecular profiling becomes more commonplace and efficient, it would be anticipated that these timelines would improve. Furthermore, if molecular diagnostics are incorporated into standard practice at an earlier time point in the patient's disease trajectory, similar to other diagnostic tests, these delays will be attenuated or eliminated. Finally, because this analysis reflected observations derived from clinical practice rather than from a controlled study, PFS could be influenced by the follow-up schedule, although most patients had restaging about every 2 months.

As molecular diagnostic tests become more sophisticated, an increasing number of abnormalities are being found. Our patients had a median of 4 molecular aberrations (range: 1–14 abnormalities) detected with the use of a next-generation sequencing panel of either 182 or 236 genes. Further complicating matters was the vast number of different abnormalities. In fact, no two patients had identical aberrations. Although the most common aberrations were *TP53* mutations (51.5% of patients) and *MYC* amplification (30.3% of patients), 15%–18% had each of *PIK3CA* mutation or amplification, *KRAS* mutation, *PTEN* loss or mutation, *CDKN2A* loss or truncation, *ERBB2* amplification, and *APC* mutation. A total of 74 genes were affected with 123 distinct aberrations. Importantly, 107 distinct abnormalities were seen only once. Of interest, one patient tested with a 50-gene hotspot panel (the Ion AmpliSeq test) showed no aberrations, whereas next-generation sequencing demonstrated 14 different aberrations. These 14 abnormalities could not have been discerned by the hotspot panel because they involved either genes not found in the panel or amplifications (hotspot panels detect point mutations). At present, it remains unclear which platforms are best suited to clinical care. For instance, the role of immunohistochemistry or other protein-based studies together with genomics might conceivably be more informative, but there are no comparative studies of this issue. Regardless, our observations highlight the uniqueness of each patient's malignancy and the need for comprehensive panels. They also indicate that therapy may require a complicated customized cocktail.

Conclusion

The complexity of the molecular landscape in most patients suggests that prosecuting these aberrations in an optimal manner will necessitate combination therapy and that refined computer programs analyzing convergence pathways and key molecular hubs may need to be incorporated into therapeutic decision making. It is also apparent that patients with advanced cancer often have multiple gene abnormalities that do not segregate well by histology. Further discerning driver abnormalities and passenger abnormalities will be crucial [34]. There is also the challenge of the relevance of the tumor sample used for the analysis. In some cases, the tissue was procured several years earlier and thus might not reflect the full spectrum of current abnormalities. Despite these limitations, current observations suggest that patients with multiple aberrations can still respond when one is targeted (although they usually relapse) and that tissue obtained even years earlier may be useful, even if not optimal [25, 26, 29, 35]. Importantly, despite all these caveats, 3 of 11 evaluable patients (27%) treated to date on the basis of the molecular diagnostic results attained a partial response, despite having progressed after three to four prior therapies in the metastatic setting. The difficulty of management informed by molecular diagnostics is illustrated by the fact that nine patients could not be treated because they were ineligible for an appropriately targeted clinical trial, they could not travel to the institution conducting the trial, insurance would not cover the cognate agents, their aberrations were not deemed actionable, or they succumbed before being able to start treatment.

Although the number of patients is still small, our observations suggest that in the era of molecular diagnostics, molecular tumor boards can bring together relevant expertise in this rapidly emerging field and may be crucial for patient care because most oncologists have not been trained in the genomics field. Optimizing therapy will require increasing access to robust clinical trials to validate molecular-based approaches and innovative measures to bring specific medications to small subsets of patients with actionable aberrations.

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Disclosures

Scott M. Lippman: Human Longevity, Inc. (C/A, OI). The other authors indicated no financial relationships.

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