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Individualized Medicine in Ovarian Cancer: Are We There Yet?

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Over the last five years, the explosion of available information regarding the molecular make up of gynecologic malignancies has yielded an optimism regarding the role of individualized medicine for our patients. Understandably, our focus has primarily rested on the most deadly of the gynecologic tumors, high grade serous ovarian cancer[1]. However, the limited “actionable” targets for this histology type have similarly resulted in limited success for biomarker-matched targeted therapy[2]. Certainly, PARP inhibition in tumors with homologous recombination deficiency sits atop the practical individualized medicine success stories in gynecologic cancer, being served not only by a widely accessible and specific biomarker, but also by the availability of targeted agents which can leverage the vulnerability[3–7]. The expanding rich molecular landscape of Type I ovarian cancer holds promise for similar success in other drug-targeting venues.

Type I (low grade) tumors of the ovary, encompassing low grade serous, clear cell, endometrioid, and mucinous adenocarcinoma, are a distinct entity from a clinical and molecular standpoint[8, 9]. In general, type I tumors are less responsive to chemotherapy, rendering them challenging clinical enigmas. Further, low grade tumors are characterized predominantly by somatic point mutations in the MAPK and PI3K pathways, rather than the diffuse genomic instability found in high grade serous ovarian cancer[2, 10–15]. These point mutations provide a wealth of molecular targets that are currently actionable with a variety of available novel agents. Thus, the exploration of a personalized medicine approach in Type I tumors is warranted.

Low grade serous ovarian cancer is known to have a high proportion of *KRAS* mutations, leading to exploration of MEK inhibition in this tumor type[10, 16]. The GOG reported a phase II trial of single agent selumetinib with modest activity and significant clinical benefit[17]. Interestingly, objective response was not associated with the presence of *KRAS* or *BRAF* mutation, although the importance of a specific mutational variant was not described. Further, association of mutation status with overall clinical benefit was not reported. Nevertheless, results of this study have led to several Phase III trials designed to compare progression-free survival of women with low grade serous ovarian cancer treated with single agent MEK inhibitors to physician choice standard of care (NCT01849874, NCT02101788).

Numerous questions remain in the implementation of biomarker-directed strategies for Type I ovarian cancer and gynecologic malignancies as a whole. 1) Is it possible to prospectively profile tumors to guide therapy choice? 2) Which molecular alterations yield sensitivity to a given targeted therapy? 3) What is most important - the molecular aberration or tumor histology? 4) Will single-agent targeted therapy be adequate? 5) How can we account for dynamic changes that occur in response to a given targeted therapy?

The manuscript by Spreafico and colleagues begins to scratch the surface of these important issues by describing the single institution experience with biomarker-directed therapy in Type I ovarian cancer[18]. Among 55 patients who underwent molecular profiling, 64% were found to have at least one somatic mutation. Of patients with a mutation, less than half were treated on a biomarker-matched clinical trial. When compared to those patients who did not receive a matched targeted therapy, patients treated with biomarker-directed treatment had a higher proportion of objective response and longer median duration of time on treatment. The 47% objective response rate is markedly higher than what has been reported for other studies of targeted therapy in Type 1 tumors[17, 19]. However, prior studies have focused on single agents, while the majority of patients on the current study were treated with a combination strategy. Of note, the only patient who progressed on a biomarker-matched agent in this study was treated with monotherapy.

As a form of commentary, the manuscript ultimately raises the specter and promise of cancer therapy based on unique features of the malignant phenotype. While focusing on genomic alternations in the tumor itself, the concept of individualized medicine has great appeal, blanketed by significant anecdotes and favorable results of large controlled trials. However, it is clear that even these unique “successes” represent, more or less, peripheral events in the larger community of cancer therapeutics – niche clusters. They are important to validate the concept and potential approach, but realistically, they represent little more, as they oversimplify both the concept and approach. The more critical need, to understand the basics of host-tumor interaction and the dynamic process of host-tumor adaptation to therapeutic intervention, lies at the heart of individualized medicine success. Unfortunately, these barriers do beg the question as to whether the paradigm can be broadened to a larger audience at the current time.

One nearly cliché term frequently used in the dialog of individualized medicine is that of “actionable” targets. The concept is, if an aberration is identified in a signaling pathway considered important to malignant phenotype and direct or downstream protein functions can be interfered with (or promoted), tumor biology will be impacted – hopefully, in the form of tumor regression. However, for this concept to have lasting success over the life of the host, it has to be considered a dynamic variable – that is, one that changes, in real-time, in response to an intervention. Protective and adaptive host and tumor responses need to be considered at the time of treatment initiation for targeted “actionable” events to have lasting impact. Consider the case of anti-VEGF therapy in ovarian cancer. Multiple phase I, II and III studies have validated the concept and approach of this treatment[20–25]. However, recurrence and progression, despite continued therapy, is the norm for most treated patients. Preclinical interrogation of adaptive response to therapy has demonstrated that factors contributing to angiogenesis “escape” include non-VEGF growth factor linked angiogenesis,

co-optive vascularization and non-angiogenesis tumor dependency[26–28]. However, it has also recently been documented that anti-VEGF induced hypoxia can promote proangiogenic tumor-associated macrophage (TAM) trafficking, leading to adaptive escape and tumor survival[29–32]. Since hypoxia is the desired goal of effective anti-angiogenesis therapy, better understanding of “how” and “when” these events occur is the first step to improving effective “actionable” targeted therapy.

Further, “actionable” is a function of biological understanding of disease and available chemistry. A classic example is the use of EGFR inhibitors in non-small cell lung cancer. Initial availability of anti-EGFR tyrosine kinase inhibitors seemed to be a good match for disease type, where EGFR was overexpressed or associated with high copy number. However, phase III trials of these agents alone, and in combination with other therapies, failed in inappropriately identified patients across a multitude of disease primaries. Later, it was discovered that specific mutations in exons 19-21 were critically important to the efficacy of these agents, and subsequent trials with more selective eligibility criteria led to the rebirth of these agents[33–35]. Certainly, targets considered “non-actionable” today might become “actionable” with better understanding of the target, its vulnerabilities and drug development. An essential integrated corollary to this concept will be identifying and exploiting the driving biology at any given time.

Perhaps the most critical piece of operationalizing truly effective individualized therapeutics is the biomarker. Biomarkers serve many purposes, but in the context of individualized medicine, they would ideally serve not only in prognostic and predictive functions guiding therapy, but also integral barometers of the intervention they are driving. In this way, they would serve to enable development of guidance algorithms on a host level, providing real-time “intel” during active therapy. Consider, for example, an assay for homologous recombination (HR) efficiency. Currently, such assays interrogate a tumor for either specific mutations in genes known to oversee the process (BRCA1/2, RAD51, PALB2, etc.) or for “evidence” of a poorly functioning HR apparatus, such as global loss of heterozygosity[4, 36]. Such findings, combined with the availability of PARP inhibitors, have ushered in a new paradigm for treating patients across a number of malignancies. However, we now know that resistance to PARP inhibitors in such individuals can occur through a number of mechanisms, many of which would not be represented if the same assays were applied[37]. Further, continuous or even repeated access to a patient’s malignancy is largely infeasible but represents a substantial handicap in leveraging even the known biology into clinical practice.

Two other aspects of individualized medicine will need to be carefully examined and thoughtfully acted upon: how should the paradigm be studied? And, what is the cost quotient for societal acceptance? It is likely that the traditional parameters of clinical investigation, including how response/failure is measured and patients are allocated to specific treatment will not be valid for an integrated individualized therapy program. Although current efforts, such as the NCI-MATCH (NCT02465060) and IMPACT-2 (NCT02152254) trials, are attempting to evaluate success of pairing tumor alteration with specific targeted agents, they are only one step in the process. If we are able to document host-tumor adaptation before tumor progression (or even in the context of objective response), we need to rethink how

these trials are constructed. For instance, the “REDIRECT” trial is poised to evaluate anti-CSF-1R therapy targeting TAMs in the context of non-progressive disease under treatment with paclitaxel and bevacizumab (NCT02923739). The premise is that lack of early objective response may represent an adaptive response by trafficking CSF-1R expressing TAMs to the microenvironment. Patients demonstrating stable disease after 2 cycles of induction therapy are randomized to addition of anti-CSF-1R therapy, with progression-free survival from randomization serving as the primary endpoint. Such non-standard trial designs based on biological events will be vital to better individualizing care.

Finally, in an era of value-based healthcare, the cost quotient of an individualized medicine program will need to be calculated and maximized. Financial costs of repeated tumor assessment may reduce over time as assays become more streamlined. However, the rising cost of targeted agents is a factor of importance, especially in light of small incremental gains in survival. Patient acceptance of testing must be factored in as well.

We applaud Dr. Spreafico and colleagues for exemplifying the potential for treatment individualization rooted in somatic tumor alterations and raising the dialog on how this concept could potentially be leveraged across gynecologic malignancies. Additional work is desperately needed though to help navigate the barriers and challenges that lie ahead. We look forward to the contributions of a global investigative effort, including the National Cancer Moonshot, to help illuminate the path to true patient-level individualized cancer therapy. Realization of the concept, is closer than it was five years ago, yet there remain multiple outstanding issues that must be addressed to reach this lofty goal.

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