Editorial

Personalized treatment of malignant mesothelioma—dream or reality?

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Malignant mesotheliomas are highly aggressive neoplasms that arise from serosal surfaces, most commonly the pleura. While these tumors are usually related to asbestos exposure, radiation for Hodgkin lymphoma or genetic alterations such as germline BRCA1 associated protein-1 (*BAP1*) inactivation syndrome, structural gene rearrangements in the Ewing sarcoma breakpoint region 1 (*EWSR1*), fused in sarcoma (*FUS*), or anaplastic lymphoma kinase (*ALK*) have been implicated in a few patients (1). Malignant mesotheliomas in general manifest many years to several decades after exposure to asbestos. Therefore, although overall relatively rare, these tumors will continue to occur despite regulatory actions and the decline in use of asbestos in some countries. In fact recent data from the Centers for Disease Control and Prevention reported that deaths related to malignant mesothelioma have increased by 4.8% between 1999 and 2015 in the United States (2). Furthermore, asbestos is a naturally occurring mineral. Therefore, people living in certain areas of the world will be continuously exposed to asbestos.

Overall survival of patients with malignant mesothelioma is poor with approximately 6 to 18 months. Surgical treatment is only an option in a small subset of patients. Most patients will undergo chemotherapy. While this treatment may prolong life and reduce symptoms, the disease is ultimately fatal. Therefore, new treatments, specifically targeted treatment agents are urgently sought to improve the outcome of these patients.

In recent years, substantial progress has been made in the understanding of molecular alterations in malignant mesothelioma. For instance loss-of-function mutations in *CDKN2A*, *NF2* and *BAP1* have been identified in malignant pleural mesotheliomas (3-6). Furthermore, a genomic analysis of 216 malignant pleural mesotheliomas revealed that genes such as *BAP1*, *NF2*, *TP53*, *SETD2*, *DDX3X*, *ULK2*, *RYR2*, *CFAP45*, *SETDB1* and *DDX51* are significantly mutated (7). In addition, recurrent mutations were discovered in *SF3B1* and *TRAF*7. Alterations in Hippo, mTOR, histone methylation, RNA helicase and p53 signaling pathways were also recognized.

These discoveries implicate a potential for a successful development of agents that can therapeutically target these altered genes and/or their respective signaling pathways. For instance, in a phase 2 clinical trial, defactinib, a focal adhesion kinase (FAK) inhibitor, was used to treat patients with malignant pleural mesothelioma with known Merlin status (NCT01870609) (8). Merlin, the product of *NF2* which is relatively frequently mutated in malignant mesotheliomas, is involved in pathways that control cell movement and proliferation. Moreover, evidence suggests that *NF2* inactivation promotes invasiveness of mesothelioma cells and that re-expression of merlin inhibits cellular functions related to the malignant properties of malignant mesothelioma cells (9). Merlin also negatively regulates FAK, a tyrosine kinase in pathways that are thought to promote cancer growth and resistance to standard chemotherapy. FAK is also overexpressed in many cancers that are associated with a low expression of merlin (10).

Unfortunately, the clinical trial using defactinib had to be terminated early as it did not improve patient outcomes.

A pharmacogenomic profiling study of 889 malignant pleural mesothelioma cell lines revealed a subgroup of cell lines that appeared highly sensitive to FGFR inhibition (11). While none of these cell lines actually harbored genomic alterations of *FGFR* family members, loss of BAP1 protein was found to be associated with enhanced sensitivity to FGFR inhibition. These findings were confirmed in a mouse xenograft model and by BAP1 knockdown and overexpression in cell line models. Gene expression analyses revealed an association between loss of BAP1 and increased expression of the receptors FGFR1/3 and ligands FGF9/18. BAP1 loss was also associated with activation of MAPK signaling. Therefore, loss of BAP1 protein enriches for a subgroup of malignant mesotheliomas that is more sensitive to FGFR inhibition. Furthermore, loss of BAP1 expression could serve as a potential biomarker to select patients who might benefit from treatment with FGFR inhibitors.

To identify genomic biomarkers for potentially treatment-responsive subsets of malignant mesothelioma Kolluri *et al.* studied whether the presence of certain mutations could predict response to existing anti-cancer compounds (12). When screening 94 drugs in 15 exome-sequenced malignant mesothelioma cell lines the authors identified a subset of malignant mesotheliomas that is defined by loss-of-function mutations of *BAP1*. This subset of malignant mesotheliomas showed an increased sensitivity to tumor necrosis factor-related apoptosis-induced ligand (TRAIL). Therefore, loss-of-function *BAP1* mutations might serve as a potential biomarker to identify malignant mesotheliomas that are likely to be sensitive to TRAIL.

In addition to its potential as biomarker, BAP1 expression has recently gained great interest for its usefulness in the distinction between malignant mesothelioma and reactive mesothelial proliferation in tissue and cytology specimens. Somatic *BAP1* mutations have been identified in 23% to 67% of malignant mesotheliomas but not in reactive mesothelial proliferations (13). *BAP1* became also known for its importance for family cancer syndromes. In fact the tumor-predisposing *BAP1* cancer syndrome has been increasingly recognized and characterized. Patients who carry that mutation are predisposed to developing multiple other tumors in addition to malignant pleural mesothelioma, including malignant peritoneal mesothelioma arising in adolescents, renal cell carcinoma, uveal melanoma, cutaneous melanoma, and atypical epithelioid Spitz tumor (14). Germline *BAP1* mutations have been described in 1% to 8% of malignant mesotheliomas (15). *BAP1*, a tumor suppressor gene, encodes a protein that is involved in the regulation of genes that are important in transcription, cell cycle control, DNA damage repair, and cellular differentiation through its deubiquitinase activity (16). In both germline or somatic settings, the pathogenic *BAP1* alterations are predominantly truncating mutations upstream of the nuclear localization sequence, leading to aberrant BAP1 protein expression with either complete absence or exclusively cytoplasmic localization in the *BAP1*-mutant tumors. Therefore, not surprising, it has been shown that BAP1 expression is lost in all cases with *BAP1* mutation (3). In addition, Bott *et al.* (3) described 8 cases of malignant mesothelioma that lacked BAP1 expression, but for which no mutation was identified. Loss of BAP1 expression is more commonly seen in epithelioid malignant mesotheliomas (68–77%) than sarcomatoid/desmoplastic mesotheliomas (0–22%) (17).

BAP1 also plays a role in epigenetic regulation and malignant transformation. BAP1 loss results in increased trimethylated histone H3 lysine 27 (H3K27e), increased enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) expression, and enhanced repression of polycomb repressive complex 2 (PRC2) targets and ultimately malignant transformation (18). Evidence suggests that loss of BAP1 expression might enhance the sensitivity of malignant pleural mesothelioma cells to therapies targeting the EZH2 oncogenic pathway (19). Preclinical studies showed that knockdown of *EZH2* in malignant pleural mesothelioma cells significantly inhibited their proliferation, migration, clonogenicity and tumorigenicity (20). These findings have led to studies using EZH2 inhibitors in the treatment of malignant mesotheliomas. For instance, a phase 2 clinical trial investigating the EZH2 inhibitor tazemetostat in malignant pleural mesotheliomas with loss of BAP1 expression who have not responded to or who have relapsed after chemotherapy completed enrollment (NCT02860286) (8).

ALK gene rearrangements have recently been identified in a few peritoneal mesotheliomas. For instance, amongst 88 patients with peritoneal mesothelioma, 3 (3.4%) cases with diffuse and strong ALK protein expression were found (21). All 3 cases were *ALK* rearranged as evaluated by fluorescence *in situ* hybridization (FISH). These peritoneal mesotheliomas were seen in women without history of asbestos or radiation exposure. In addition, 2 of the 3 women were under the age of 40 years. An additional 8 peritoneal mesotheliomas showed weak ALK expression.

In these cases, FISH did not reveal a rearrangement of the *ALK* gene. These findings suggest that ALK expression might be a biomarker to identify peritoneal mesotheliomas that harbor an *ALK* rearrangement and potentially are considered for tyrosine-kinase inhibitor therapy. However, clinical trials to test the effectiveness of *ALK*-rearrangement-targeted therapy in peritoneal mesotheliomas are still needed.

Evidence suggests that a subset of malignant pleural mesotheliomas is deficient in argininosuccinate synthetase 1 (ASS1). ASS1 is known to be a rate-limiting enzyme in the production of arginine, a precursor to molecules that are important in tumorigenesis. Decrease or absence of expression of ASS1 has been found in 63% of malignant pleural mesotheliomas (22). The viability of ASS1-deficient malignant pleural mesothelioma cell lines grown in arginine-free medium markedly declined over a few days while cell lines with preserved ASS1 expression were not affected. Overall evidence suggests in malignant pleural mesotheliomas and other tumors that arginine deprivation is lethal in ASS-negative tumors (23). In a prospective randomized phase 2 trial including ASS1-deficient malignant pleural mesotheliomas patients received either ADI-PEG20, a pegylated arginine deiminase, plus best supportive care (n=44) or best supportive care only (n=24) (23). Patients who received ADI-PEG20 and best supportive care had a significant longer median progression free survival of 3.2 months compared with 2.0 months of the control group. A dose-escalation phase 1 study included patients with ASS1-deficient malignant pleural mesothelioma and non-small cell lung carcinoma who were treated with ADI-PEG20 together with pemetrexed and cisplatin (24). Stable disease was observed in all patients; 78% of patients achieved a partial response. One of the patients who showed partial response had a sarcomatoid pleural mesothelioma, one of the most aggressive tumors. These results suggest that the combination of standard chemotherapy and arginine deprivation in patients with ASS1-deficient malignant mesotheliomas might be superior to chemotherapy alone. However, subsequent larger prospective randomized trials are necessary to support that finding. In fact, a phase 2/3 trial is currently recruiting patients with malignant pleural mesothelioma with low ASS1 expression (ATOMIC-Meso phase 2/3 study).

Although malignant mesotheliomas are rare, considerable progress has been made in the identification of genetic alterations and some of their associated, potentially affected pathways. Using that approach, candidate genes and pathways that might be specifically targeted with particular agents have been identified and will be identified. Although some treatments failed, others are actively under investigation with promising outcomes. While still a dream a few years ago, targeted therapy of malignant mesotheliomas is becoming a reality.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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