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ASO AUTHOR REFLECTIONS

ASO Author Reflections: The Disease-Free Interval is Associated with Oncologic Outcomes for Patients with Recurrent Gastrointestinal Stromal Tumor

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PAST

For patients with resected gastrointestinal stromal tumor (GIST), several prognostic tools are available to predict recurrence and form the basis for recommending adjuvant imatinib therapy.[1,2] Patients with high-risk tumors most frequently experience recurrence after completing adjuvant tyrosine kinase inhibitor (TKI) therapy ($\leq$ 90 %) rather than during treatment. Additionally, patients with recurrent GIST can display a wide range of outcomes, including survival and time to imatinib resistance, even amongst patients with identical driver mutations and seemingly similar patterns of recurrence. To date, supportive data enabling clinicians to predict prognosis accurately after GIST recurrence are sparse.[3] Ultimately, the inability of clinicians to prognosticate hinders their ability to counsel patients regarding the role of continued TKI treatment versus resection of recurrent disease. Additionally, factors leading to the development of secondary TKI resistance are poorly understood, although this is a key event for patients with recurrent disease and those with metastatic disease at diagnosis.

PRESENT

This report describes the authors' retrospective analysis of patients with recurrent GIST at their NCI Comprehensive Cancer Center. The disease-free interval (DFI) from the end of oncologic therapy (either resection or adjuvant therapy) was identified as a key factor associated with progression and mortality.[4] The timing of this end point (the end of oncologic therapy) was purposefully chosen to account for the unique disease biology of GIST, a sarcoma that rarely recurs during adjuvant therapy (typically administered for 3 years). The milestone of 2 years or longer to recurrence after the end of oncologic therapy (reached by one third of the patients in this study) identified a cohort with excellent long-term progression-free and overall survival. The authors believe this finding will be useful for informing patients and providers about the likely disease course and treatment choices upon recurrence (e.g., considering resection of recurrent disease). Additionally, the study findings may provide insights to deepen understanding of secondary imatinib resistance through direct comparison of patients with early versus late recurrent GIST—ends of a sarcoma spectrum that reflect dramatically different disease trajectories. The predictive utility of the DFI has been established for several other cancer types such as esophageal cancer[5] and metastatic colorectal cancer to the liver. However, the prognostic impact of the DFI in visceral sarcomas such as GIST has not been reported.

FUTURE

To date, researchers and clinicians do not fully understand the entirety of prognostic factors in patients with recurrent GIST. Moving forward, the authors encourage multi-institutional studies of patients to form a cohort of

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patients with recurrent GIST sufficiently large enough to create and validate prognostic nomograms for this population. Collaborative efforts also are needed to update current nomograms for predicting recurrence in patients with resected GIST, accounting for prior TKI therapies. Tyrosine kinase inhibitor-based therapy for patients with GIST is rapidly evolving, with the continued emergence of new agents to treat this disease, often directed to a specific driver mutation. Additionally, the authors recognize that more work is needed to determine the optimal postoperative surveillance given the prognostic differences of patients with recurrent GIST. One size does not fit all for this disease. Given the rarity of recurrence during adjuvant therapy, perhaps surveillance may safely be performed less frequently until the end of therapy? Then, after completion of adjuvant therapy, more intense surveillance could continue until an optimal prognostic time point, such as 2 years, after which the surveillance interval could be relaxed due to the excellent prognosis of patients recurring after this interval. Finally, and most importantly, the research community needs to continue investigations into GIST tumor biology to better understand the molecular underpinnings in patients with early versus late recurrent GIST. Ultimately, the authors believe these data will provide fundamental insights into the mechanisms driving the development of imatinib resistance in patients with recurrent and primarily metastatic GIST. Until then, the disease-free interval from the end of oncologic therapy may be the best method for predicting future tumor behavior of this unique visceral sarcoma.

DISCLOSURE

Michael Heinrich is a consultant for Deciphera Pharmaceuticals, Novartis, Blueprint Medicines, and Theseus Pharmaceuticals. The remaining authors have no conflicts of interest.

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