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# Initiative for Molecular Profiling and Advanced Cancer Therapy and challenges in the implementation of precision medicine

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ABSTRACT

In the last decade, breakthroughs in technology have improved our understanding of genomic, transcriptional, proteomic, epigenetic aberrations and immune mechanisms in carcinogenesis. Genomics and model systems have enabled the validation of novel therapeutic strategies. Based on these developments, in 2007, we initiated the IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy) study, the first personalized medicine program for patients with advanced cancer at The University of Texas MD Anderson Cancer Center. We demonstrated that in patients referred for Phase I clinical trials, the use of tumor molecular profiling and treatment with matched targeted therapy was associated with encouraging rates of response, progression-free survival and overall survival compared to non-matched therapy. We are currently conducting IMPACT2, a randomized study evaluating molecular profiling and targeted agents in patients with metastatic cancer. Optimization of innovative biomarker-driven clinical trials that include targeted therapy and/or immunotherapeutic approaches for carefully selected patients will accelerate the development of novel drugs and the implementation of precision medicine.



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Precision medicine is a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. Initially, the term "precision medicine" was used to describe targeting tumor molecular abnormalities with drugs known to inhibit the function of a molecular alteration. In recent years, precision medicine has included the development of therapeutic agents that target any biological abnormality that is associated with the development of cancer. Consequently, owing to recent major breakthroughs in immunotherapeutic strategies, the armamentarium of the precision medicine approach now also includes immunotherapy.

The identification of pathways involved in the pathophysiology of carcinogenesis, metastasis, and drug resistance, as well as the emergence of technologies enabling tumor molecular analysis and the discovery of targeted therapies has stimulated research focusing on the optimal use of targeted agents. The discovery of imatinib for the treatment of Philadelphia chromosome–positive chronic myeloid leukemia[1] prompted researchers to identify molecular aberrations in solid tumors.[2-7]

In 2007, we initiated the Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) study, the first personalized medicine program for patients referred to the Phase I Clinic at The University of Texas MD Anderson Cancer Center (Houston, TX).[8] Our goal was to assess whether molecular analysis of advanced cancer to select targeted therapy to counteract the effects of specific aberrations would be associated with improved clinical outcomes. Patients with advanced cancer were treated based on their molecular analysis. Patients whose tumors had an aberration were treated with matched targeted therapy, when available. Treatment assignment was not randomized. In this retrospective analysis, the clinical outcomes of patients with molecular aberrations treated with matched targeted therapy were compared with those of consecutive patients who were not treated with matched targeted therapy. Of 1144 patients analyzed, 460 (40.2%) had 1 or more aberration. In patients with 1 molecular aberration, matched therapy ($n = 175$) compared with treatment without matching ($n = 116$) was associated with a higher overall response rate (27% vs 5%; $P < 0.0001$), longer time-to-treatment failure (TTF; median, 5.2 vs 2.2 months; $P < 0.0001$), and longer survival (median, 13.4 vs 9.0 months; $P = 0.017$). Matched targeted therapy was associated with longer TTF compared with their prior systemic therapy in patients with 1 mutation (5.2 vs 3.1 months, respectively; $P < 0.0001$). In multivariate analysis in patients with 1 molecular aberration, matched therapy was an independent factor predicting response ($P = 0.001$) and TTF ($P = 0.0001$).[8]

Next, we reported validation and landmark analyses in a subsequent set of patients treated with the personalized medicine approach in our phase I program at MD Anderson.[9,10] Outcomes of patients who were referred for treatment on phase I clinical trials at MD Anderson from March 2011 to January 2012 were compared between those who had received targeted therapy and those for whom no targeted therapy was available. Two-month landmark analyses for overall and progression-free survival (PFS) combining previously published and validation cohort patient data were performed. The landmark method was used to avoid selection bias in the correlation of survival or PFS with response by type of therapy (matched therapy vs nonmatched therapy).[11,12] By this method of evaluating outcome, patients who die early do not prejudicially influence the analysis of a postdiagnosis endpoint.[11,12] In patients with one alteration, matched therapy ($n = 143$) compared with treatment without matching ($n = 236$) was associated with a higher objective response rate (12% vs 5%; $P < 0.0001$), longer PFS (median, 3.9 vs 2.2 months; $P = 0.001$), and longer survival (median, 11.4 vs 8.6 months; $P = 0.04$). In multivariate analysis, matched therapy was an independent factor predicting response ($P = 0.015$) and PFS ($P = 0.004$). The 2-month landmark analyses in the matched therapy group demonstrated that the median survival of responders was 30.5 months compared with 11.3 months for nonresponders ($P = 0.01$); and the median PFS was 38.7 months compared with 5.9 months, respectively ($P < 0.0001$). The respective values in the nonmatched therapy group were 9.8 and 9.4 months ($P = 0.46$) and 8.5 and 4.2 months ($P = 0.18$). This validation analysis confirmed our previous observations.[10]

In May 2014, we started Initiative for Molecular Profiling and Advanced Cancer Therapy 2 (IMPACT 2),[9,13] a randomized study evaluating molecular profiling and targeted agents in