Shri Ramniklal J. Kinarivala Cancer Research Award - 2024

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Translational Research to Transformative Medicine

Treatment of solid and liquid malignancies has constantly been challenging because resistance develops and disease reoccurs or transforms to more aggressive form. This information underscores a need for continuous translational research for patients with cancer. At MD Anderson Cancer Center, our motto is 'Research-driven patient care'; and this research is clinical or translational research.

Throughout my career at MD Anderson Cancer Center, I have focused on translational research especially in hematological malignancies. The major objective of my research program is to improve the therapeutic activity of anticancer drugs by understanding their metabolism, mechanisms of action and interactions in combinations. This approach provides the basic scientific knowledge about these compounds and furnishes important information in the design of new clinical protocols. Below I provide three examples where research in my group resulted in changing clinical practice for treatment of different leukemias.

First example:
Biochemical modulation of cytarabine for patients with acute myelogenous leukemia (AML):
Cytarabine or ara-C, a nucleoside analog, is the most effective agent for treatment of AML. This drug is metabolized to its triphosphate; ara-CTP (cytotoxic metabolite) and for this conversion, the rate-limiting step is catalyzed by enzyme deoxycytidine kinase (dCK). Activity of dCK is feed-back inhibited by deoxycytidine triphosphate or dCTP. Fludarabine, another nucleoside analog, also gets accumulated as triphosphate. Fludarabine triphosphate inhibits ribonucleotide reductase resulting in lowering of deoxynucleotide pools including dCTP. We hypothesized, that fludarabine incubations prior to cytarabine will result in increased ara-CTP and better clinical responses. We tested and validated this hypothesis in cell lines and primary leukemia cells. Based on our in vitro data in cell lines and ex vivo studies in primary cells, in collaboration with Dr. Elihu Estey in the Leukemia Department, clinical trials were designed with a pharmacologically guided sequential combination of fludarabine and ara-C for patients with relapsed acute and chronic leukemias. The pharmacokinetic and pharmacodynamic endpoints studied during therapy provided knowledge for optimal schedule, drug dosage and duration of infusions for this regimen. The biochemical and clinical success of this trial in relapsed acute leukemia (AML) resulted in moving this regimen to treat patients with de novo AML. This strategy has been employed nationally and internationally. Still, today; fludarabine and cytarabine couplet has remained backbone of AML therapy especially for core-binding factor AML.

Second example:
Identification of Nelarabine for T-cell Acute lymphoblastic leukemia (T-ALL) & lymphoma (T-LBL):
Clinical observation in pediatric patients demonstrated that children with purine nucleoside phosphorylase deficiency leads to T-lymphopenia. Laboratory studies identified accumulation of deoxyguanosine triphosphate specifically in T-cells leading to T-cell death. This resulted in synthesis of deoxyguanosine analog, arabinosylguanine, ara-G. Nelarabine, 2-amino-6-methoxy-arabinosyl guanine, is more soluble prodrug that gets converted to ara-G. My laboratory investigated actions of G-analogs, such as arabinosylguanine and nelarabine (GW506U78). Our Phase I investigations in collaboration with Dr. Keating established this agent as a future drug for relapsed/refractory T-ALL. Cellular pharmacokinetic investigations in circulating leukemia cells during

therapy demonstrated that the clinical success of the drug was strongly associated with accumulation of analog triphosphate. Using molecular and biochemical approaches, we identified the differences in the actions of ara-G for T and B, and lymphoid versus myeloid diseases. Our laboratory and clinical endpoints established the mechanisms of this specificity. This drug was approved by the U.S. Food and Drug Administration (US-FDA) for T-ALL and T-LBL and was recently tested in phase III randomized trials.

Third example:

Mechanism-based combination of ibrutinib & venetoclax for chronic lymphocytic leukemia (CLL):

B-Cell receptor (BCR) pathway is responsible for production, proliferation, survival and migration of B-cells including chronic lymphocytic leukemia cells, which is a B-cell malignancy. Bruton's tyrosine kinase (BTK) is a pivotal enzyme in BCR signaling. Ibrutinib binds to cysteine 481 residue in the kinase domain of BTK and irreversibly inactivates the protein. Single agent ibrutinib was successful in long-term progression-free survival of patients with CLL but resulted in very limited complete remissions (CR) and undetectable measurable residual disease (uMRD). The clinical success of ibrutinib and its limitations suggested that combination strategies will be needed to achieve deeper and potentially complete remission which may result in uMRD status; a desired clinical endpoint that may translate in cure. Molecular research during clinical trial from my group suggested that the peripheral blood CLL cells after ibrutinib therapy have high levels of Bcl-2 anti-apoptotic proteins while levels of Mcl-1, other congener protein of the same family, are declined. This information provided a strong biochemical rationale to combine ibrutinib with Bcl-2 antagonist, venetoclax. To validate this hypothesis, we performed several in vitro, ex vivo and in vivo mouse model experiments to establish utility of this combination and pharmacological rationale to combine these two agents. Clinically, it was apparent that ibrutinib targets CLL cells resident in lymph nodes while venetoclax irradicates leukemic lymphocytes from peripheral blood and bone marrow providing clinical rationale to combine these two drugs. In collaboration with my clinical colleagues (Dr. Nitin Jain and Dr. Bill Wierda), we initiated a clinical protocol and treated 120 treatment-naive and 80 previously treated high-risk CLL. Early results as well as 3.5-year follow-up studies suggest achievement of complete remission and MRD negativity. This is the first time in CLL we have achieved uMRD with targeted therapeutics. Importantly, both drugs are oral formulation making it convenient outpatient therapy. This combination was then tested in the USA and in a randomized investigation in Europe; it is approved by European Medicines Agency (EMA).

Above three examples serve as epitome of translational research where bench to bedside and back have made transformative changes for patients with leukemias. Considering complexity of cancers, plasticity of cancer cells and their interactions with microenvironment underscore a continuous need for translational research to conquer cancer.

Publications from Gandhi group

First Example:

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