Title

Optimization of Acute Lymphoblastic Leukemia Patient Regimens Using a Phenotypic Personalized Medicine Digital Health Platform

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Optimization of Acute Lymphoblastic Leukemia Patient Regimens Using a Phenotypic Personalized Medicine Digital Health Platform

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Bioengineering

by

Theodore Wonpeum Kee

2017

ABSTRACT OF THE THESIS

Optimization of Acute Lymphoblastic Leukemia
Patient Regimens Using a Phenotypic Personalized Medicine
Digital Health Platform

by

Theodore Wonpeum Kee

Master of Science in Bioengineering
University of California, Los Angeles, 2017
Professor Dean Ho, Chair

Acute lymphoblastic leukemia (ALL) is a blood cancer that is characterized by overproduction of lymphoblasts in the bone marrow. Treatment for ALL typically uses combination chemotherapy. However, a major challenge for combination therapy is the inability to pinpoint drug doses that are optimized for each patient. To address this challenge, we have developed a powerful digital health technology platform based on the field of Phenotypic Personalized Medicine (PPM). PPM identifies patient-specific maps that correlate drug inputs with phenotypic outputs parabolically. In a disease mechanism-independent fashion, PPM was able to determine individualized drug ratios/dosages for 2 ALL patients in this study using a retrospective optimization approach. This optimization process demonstrated that dynamically adjusted dosing

of combination chemotherapy can enhance treatment outcomes while also substantially reducing the amount of chemotherapy that is required. This may lead to shortened maintenance therapy regimens that will in turn, reduce the onset of complications following remission.

The thesis of Theodore Wonpeum Kee is approved.

Chih-Ming Ho

Dino Di Carlo

Dean Ho, Committee Chair

University of California, Los Angeles

2017

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ACKNOWLEDGEMENTS

Chapter One is a version of Dong-Keun Lee, Vivian Y. Chang, Theodore Wonpeum Kee, Chih-Ming Ho, and Dean Ho, Optimizing Combination Therapy for Acute Lymphoblastic Leukemia Using a Phenotypic Personalized Medicine Digital Health Platform: Retrospective Optimization Individualizes Patient Regimens to Maximize Efficacy and Safety, SLAS Technology, Vol. 22(3) 276–288. Copyright © 2016 Society for Laboratory Automation and Screening. Reprinted by permission of SAGE Publications. DOI: 10.1177/2211068216681979 journals.sagepub.com/home/jla

Dong-Keun Lee, Vivian Y. Chang, Theodore Wonpeum Kee, Chih-Ming Ho, and Dean Ho used the anonymized clinical data provided by the clinical team to perform the PPM analysis and optimization; constructed the 4-drug and 2-drug interaction maps, analyses, and interpretations; wrote the nonpatient clinical assessment portions of the manuscript; and critically revised the manuscript. Vivian Y. Chang, Theodore Wonpeum Kee, and Dean Ho coordinated IRB approval documentation and approval. Vivian Y. Chang wrote the patient clinical assessment portions of the manuscript and performed the clinical data collection and anonymization.

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CHAPTER 1:
OPTIMIZING COMBINATION THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA USING A PHENOTYPIC PERSONALIZED MEDICINE DIGITAL HEALTH PLATFORM: RETROSPECTIVE OPTIMIZATION INDIVIDUALIZES PATIENT REGIMENS TO MAXIMIZE EFFICACY AND SAFETY

1.1 Introduction

Treatment for ALL typically consists of multiple stages including remission induction, intensification, and maintenance therapy. [1-3] While the drugs and their corresponding utilized during these stages are well established, the protocols for administering these therapies are often based off of maximum tolerated dosage (MTD) from initial dose escalation studies. In addition, disease mechanism or drug targets have been used to select therapies for patient care. [4-8] These approaches, while historically important, do not pinpoint drug-dose ratios, implicitly precluding

the personalization of care and optimization of treatment outcomes. In fact, intensification of therapy, when not optimally administered, may increase the risk of relapse in pediatric ALL. [3] This is a challenge that has confronted nearly every discipline of medicine, ranging from oncology to infectious diseases and cardiovascular medicine, among many others. Previous studies have identified promising approaches towards multi-drug optimization, both in the context of drug development as well as individualizing patient treatment. However, these approaches often utilize drug pairing to predict the efficacy of multi-drug combinations, which precludes absolute and dynamic optimization in patients. To overcome this major barrier, we have developed a powerful digital health technology platform based on the field of Phenotypic Personalized Medicine (PPM). [9-15] PPM effectively calibrates the patient response to therapy to construct a parabolic map that is unique to each patient. PPM does not require algorithms, predictive modeling, or machine learning, and is capable of dynamically optimizing therapy for the entire duration of care. This is particularly important, since drug synergism and antagonism is dose-dependent, and can vary within the same patient over the course of treatment within the same patient. [16] This study examined the administration of 4-drug maintenance therapy regimens (dexamethasone, vincristine, mercaptopurine (6MP), and methotrexate) in 2 patients. The doses of these drugs served as the inputs while maintaining absolute neutrophil count (ANC) and platelet counts within target ranges served as the outputs for optimization. We utilized PPM to construct personalized parabolic response maps for each patient to retrospectively optimize their regimens to successfully eliminate ANC and platelet deviations outside of their respective target ranges. PPM is not limited by the number of drugs that can be optimized. Therefore, both 4-drug and 2-drug (6MP and methotrexate) optimization regimens were identified as a demonstration of disease biology and mechanism-independent multi-drug optimization. In

addition, patient-specific drug response maps were constructed, revealing individualized drug synergism/antagonism that was dose-dependent. Finally, analysis of the contribution of drug-drug interaction terms (ITA) and second-order (SOT) terms was conducted in parallel with clinical and PPM-optimized dosing regimens, revealing the importance of maintaining threshold ITA levels to eliminate target ANC and platelet count deviations. These clinical data-backed readouts provide actionable guidance to maintain patient-specific and dynamically optimized combination therapy regimens for the entire duration of treatment. As such, PPM represents a powerful and broadly applicable digital health technology platform to optimize treatment for a broad array of disorders.

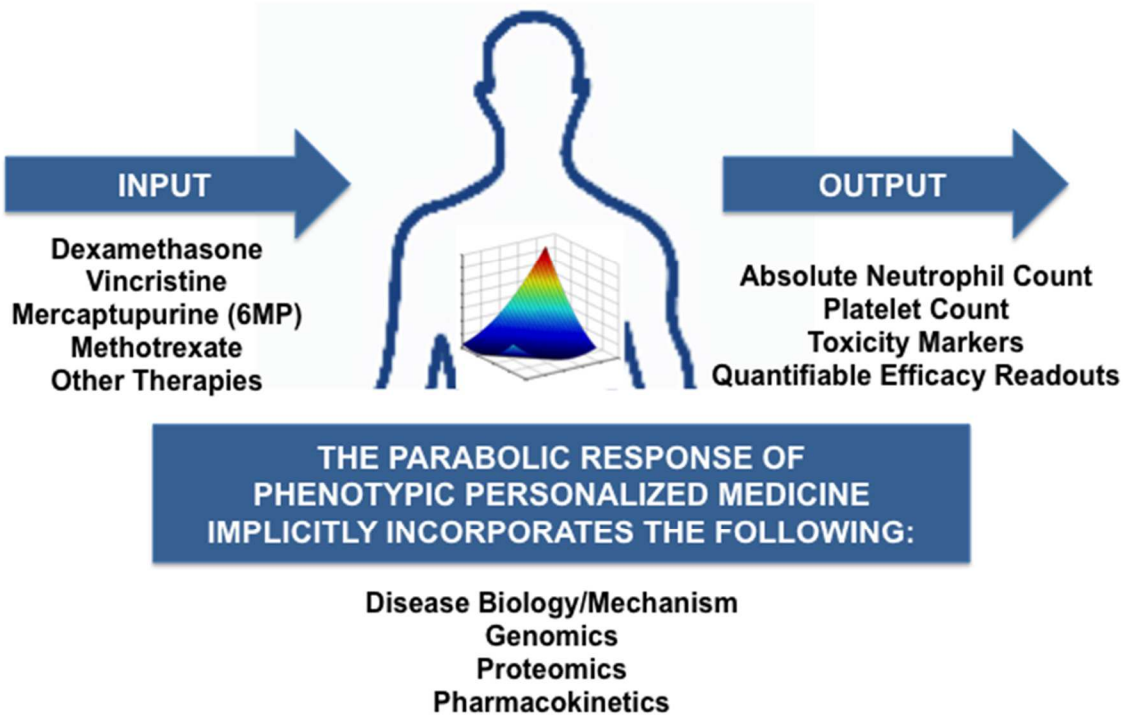

Figure 1-1. Schematic of Phenotypic Personalized Medicine (PPM). The primary components of PPM are the inputs, comprised of the therapies, and the outputs, which are quantifiable indicators of treatment efficacy and safety.

1.2 Materials and Methods

1.2.1 Acute Lymphoblastic Leukemia Patient Data

This study was conducted under approved Institutional Review Board (IRB) protocol number IRB#16-000723. Data obtained included drug dosages for dexamethasone, mercaptopurine, vincristine, and methotrexate and corresponding time points (e.g. Days 28, 57, 85, 113, 148, 176, 211, 242, 270, 302, 330). Absolute neutrophil count (ANC) and platelet counts corresponding to the respective drug dosing dates were also identified for optimization.

1.2.2 Phenotypic Personalized Medicine (PPM)-Based Optimization

To identify PPM-optimized chemotherapy dosages, a patient-specific 2^{nd} order polynomial map was constructed from linear regression using variables including drug dosages, absolute neutrophil counts (ANC), and platelet counts. In addition, individualized second order effects and drug-drug interaction terms were assessed in correspondence with measured and PPM-optimized ANC and platelet values. PPM 2-D and 3-D drug interaction maps were plotted using MATLAB R2014a (MathWorks, Inc.) with a matrix input of drug concentration values correlated to platelet counts or ANC. [16]

1.3 Results and Discussion

1.3.1 Clinical Optimization of Combination Therapy Using Mechanism-Independent Digital Health Technology

The implementation of PPM is based on the foundation that a patient's phenotypic response (output) to drug treatment (input) can be represented by parabolic response surface. Phenotypic responses can include tumor burden, bacterial/viral load, international normalized ratio (INR), serum toxicity indicators (e.g. myelosuppression, serum alanine aminotransferase,

etc.), or a combination of these readouts. This parabolic response map is defined by patient-specific constants in a quadratic expression (Figure 1-1). [16] This holds true for all patients and all indications. The significance of the parabolic response surface is based on its ability to identify exactly where the best dosing parameters exist at any given time during treatment. PPM allows this response surface to be continually optimized during care as regimen changes occur, or the patient undergoes additional procedures. Furthermore, this phenotypic map implicitly incorporates mechanistic components that drive treatment outcomes, such as disease biology, genetics, proteomics, and pharmacokinetics. Therefore, explicit knowledge pertaining to these elements is not required to mediate continuously optimization.

1.3.2 Dynamic Optimization of Personalized Combination Therapy (4-drug)

Conventional maintenance therapy involves the modulation of 6MP and methotrexate in order to maintain ANC and platelet levels within target levels. Titration is often used as the primary means of adjusting the doses of these two therapies. However, clinical titration has shown that the proper dosing of even one drug can be challenging. [16] Therefore, due to barriers that prevent rational dosing of multiple drugs, let alone optimized multi-drug administration, a technology platform such as PPM may be particularly important for improving response rates in oncologic indications.

Since PPM is not limited by the number of drugs in a regimen, we conducted a 4-drug optimization assessment for 2 patients. For patient 1, clinical chemotherapy administration resulted in substantial deviation from the ANC target range on day 85, and deviations on days 242 and 302, and platelet levels that remained within the target range. In contrast, PPM-

optimized administration of dexamethasone, 6MP, vincristine, and dexamethasone eliminated the ANC deviations while also maintaining normal platelet levels (Fig. 1-2). In comparing the clinical and PPM-optimized administration of each drug PPM optimization resulted in substantially lower dexamethasone administration compared to clinical dosing. In fact, PPM-optimized dexamethasone and 6MP dosages were approximately 4-fold lower than the clinically administered dosages. Initial vincristine dosing was higher for the PPM-optimized regimen compared to clinical dosing. However, PPM optimization identified substantially lower dosages of vincristine compared to clinical administration starting on day 211 (with the exception of day 270) through the end of treatment that eliminated ANC deviations. PPM suggested 6MP dosing resulted in sharply lower drug dosages compared to clinical administration starting on day 148, while PPM-guided methotrexate dosing was sharply lower than clinical dosing parameters on day 302.

In patient 2, clinical chemotherapy resulted in a substantial deviation from the ANC target range that spanned from day 148 to 176 while platelet levels remained within the target range during the course of treatment. To eliminate this ANC deviation, PPM optimization resulted in a steady decrease in dexamethasone dosing over time compared to clinical administration that alternated between dosage increases and decreases. PPM-suggested vincristine dosages alternated between being higher and lower than clinically-prescribed dosages. However, PPM-optimized 6MP and methotrexate dosages were notably lower than the clinically administered dosages for virtually the entire duration of care (Fig. 1-3).

While 4-drug modulation is currently not utilized for ALL maintenance therapy, this optimization study demonstrated that PPM is uniquely capable of dynamically personalizing the

administration of all 4 drugs to optimize dosing to prevent ANC deviations for the entire duration of care.

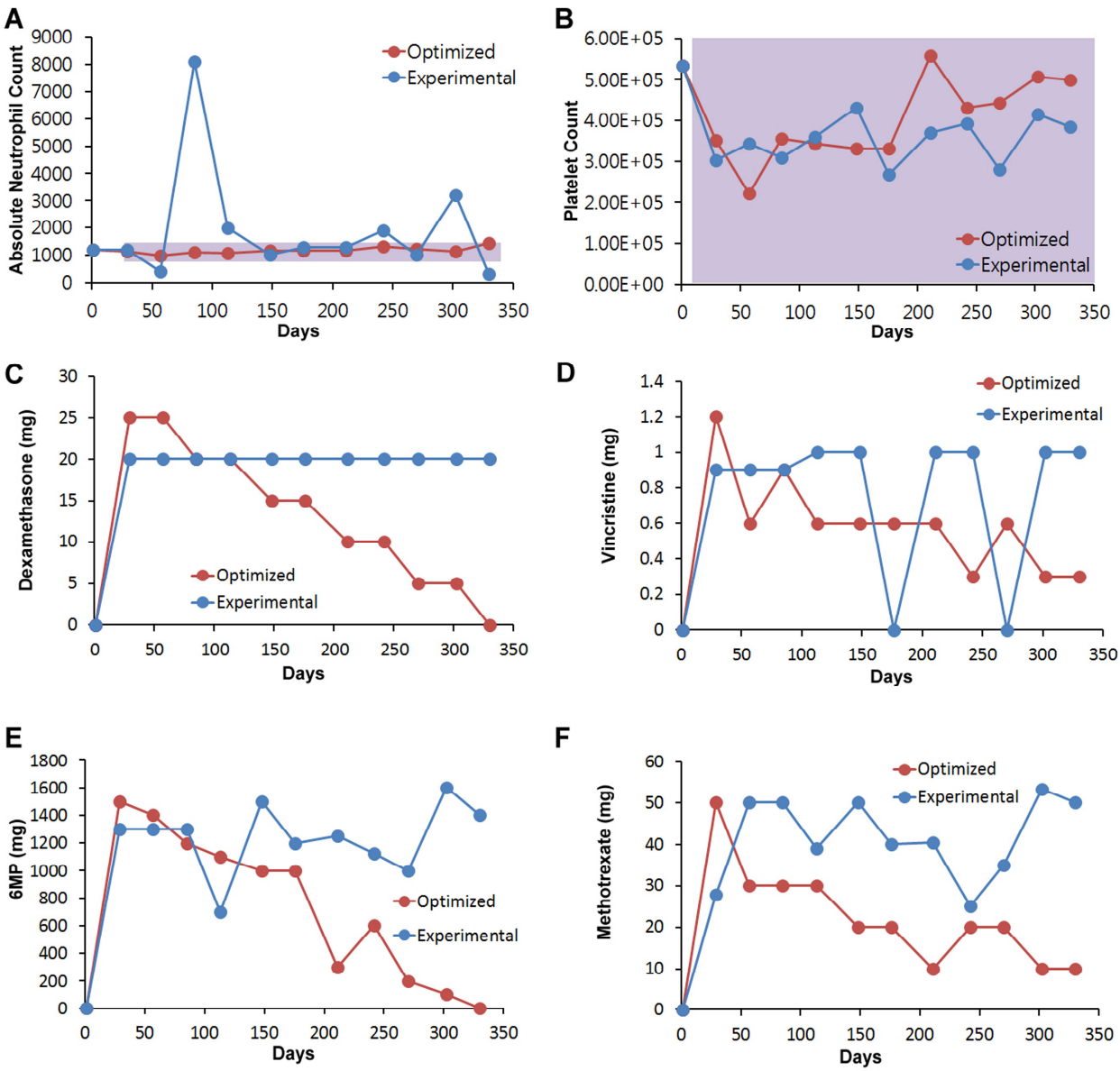

Figure 1-2. Patient 1's Phenotypic Personalized Medicine (PPM)-optimized and clinically administered 4-drug regimens. (A) Patient 1 comparison of PPM-optimized and clinical absolute neutrophil count. (B) Patient 1 comparison of PPM-optimized and clinical platelet levels. (C) Patient 1 comparison of PPM-optimized and clinical dexamethasone dosing regimen. (D) Patient

1 comparison of PPM-optimized and clinical vincristine regimen. (E) Patient 1 comparison of PPM-optimized and clinical 6MP regimen. (F) Patient 1 comparison of PPM-optimized and clinical methotrexate regimen.

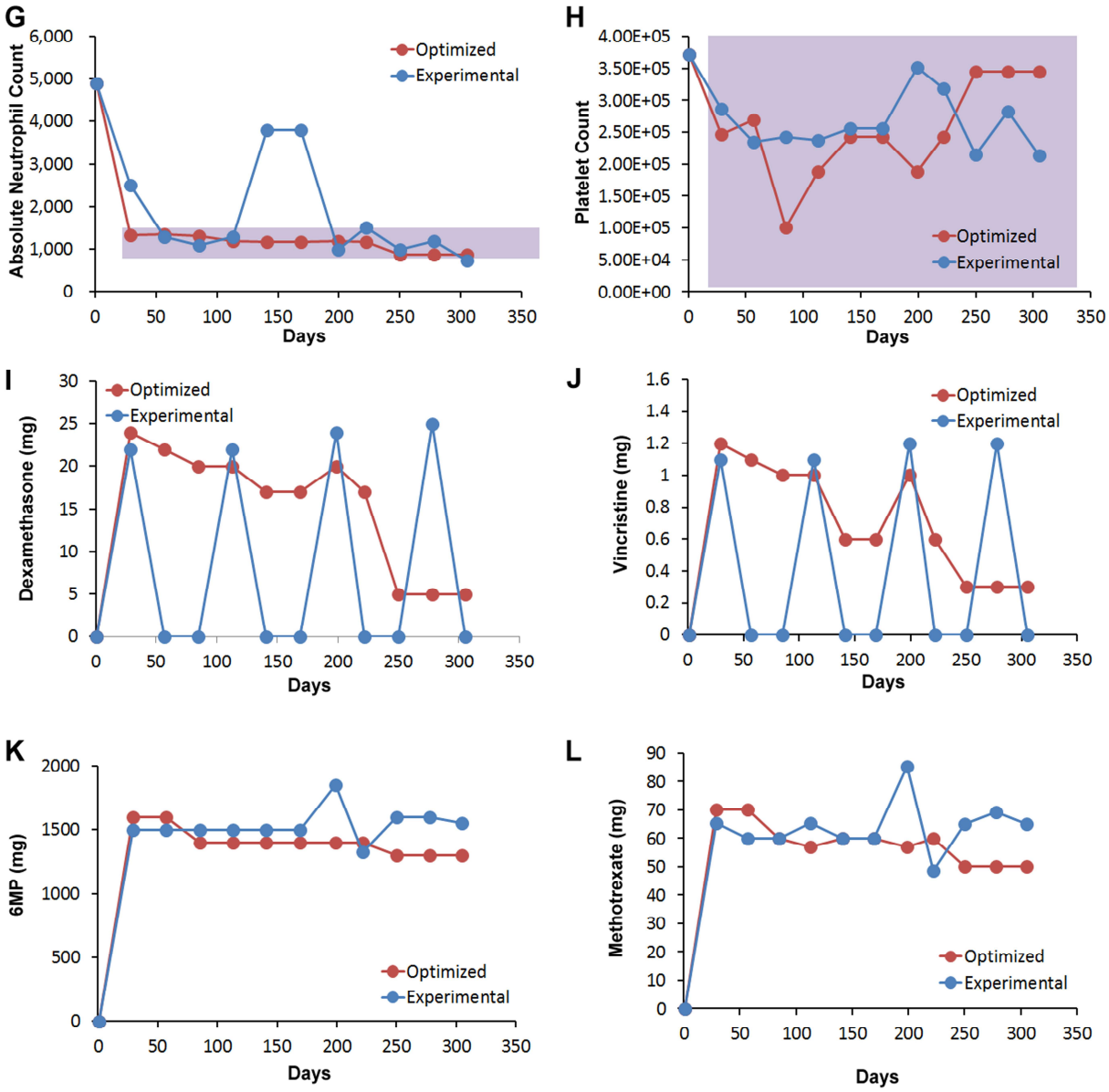

Figure 1-3. Patient 2's Phenotypic Personalized Medicine (PPM)-optimized and clinically administered 4-drug regimens. (A) Patient 2 comparison of PPM-optimized and clinical absolute neutrophil count. (B) Patient 2 comparison of PPM-optimized and clinical platelet levels. (C) Patient 2 comparison of PPM-optimized and clinical dexamethasone dosing regimen. (D) Patient

2 comparison of PPM-optimized and clinical vincristine regimen. (E) Patient 2 comparison of PPM-optimized and clinical 6MP regimen. (F) Patient 2 comparison of PPM-optimized and clinical methotrexate regimen.

1.3.3 Dynamic Optimization of Personalized Combination Therapy (2-drug)

A 2-drug PPM optimization study to modulate 6MP and methotrexate was also performed. In patient 1, the elimination of ANC deviations was achieved by 6MP doses, that with the exception of days 113 and 242 where PPM recommended a higher dose as well as a comparable dose at day 270, were notably lower than the clinically-administered dosages. PPM-determined methotrexate dosages were also notable lower for a vast majority of the treatment period (Fig. 1-4).

In patient 2, the disparity in dosing recommendations were more apparent between the PPM-determined and clinically administered protocols. For both 6MP and methotrexate, the PPM-optimized dosages were lower than the clinically administered dose for virtually the entire duration of care. In some cases, the PPM-determined dose was approximately 40% lower compared to the clinical dose (Fig. 1-4).

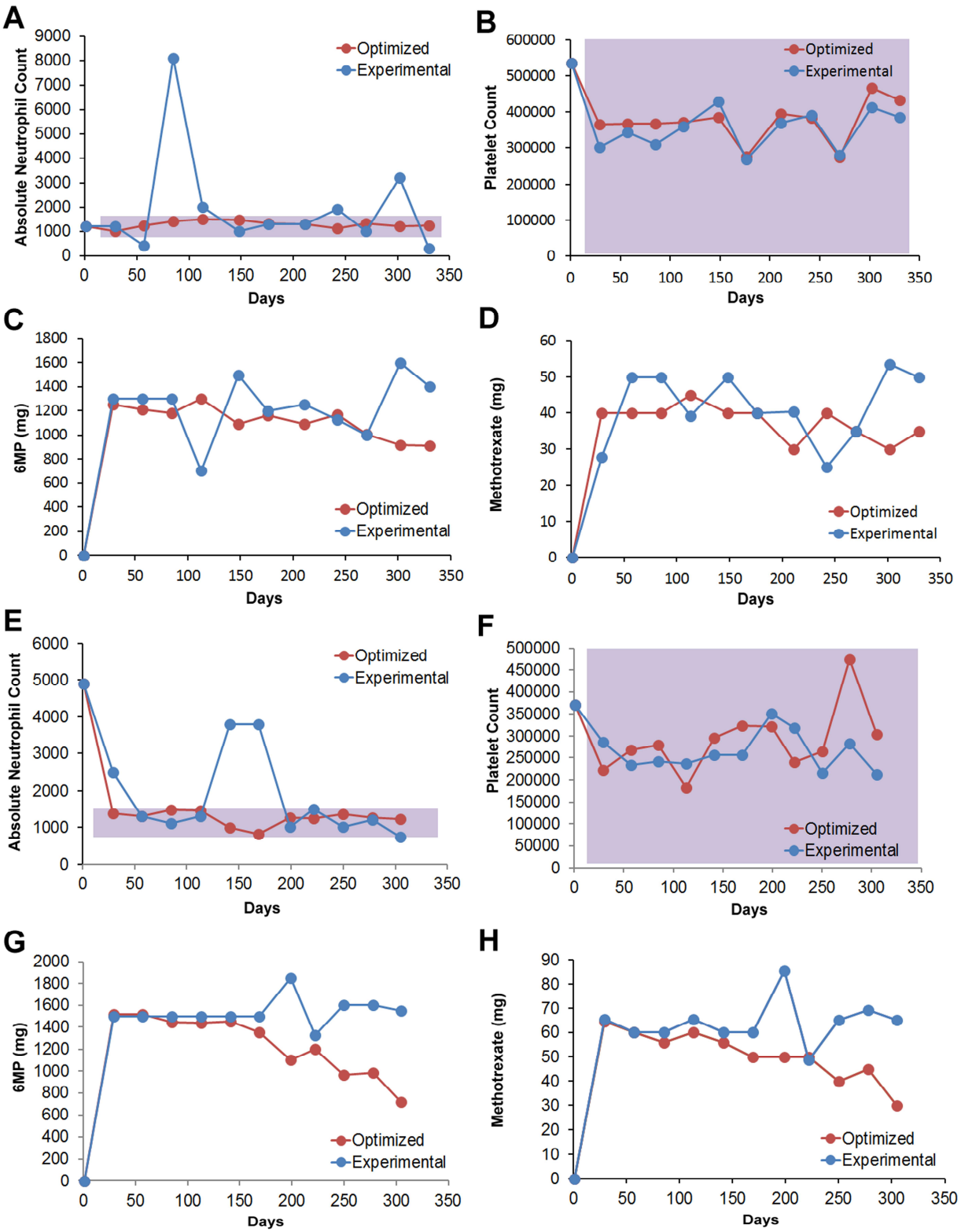

Figure 1-4. Phenotypic Personalized Medicine (PPM)-optimized and clinically administered 2-drug regimens. (A) Patient 1 comparison of PPM-optimized and clinical absolute neutrophil

count. (B) Patient 1 comparison of PPM-optimized and clinical platelet levels. (C) Patient 1 comparison of PPM-optimized and clinical 6MP dosing regimen. (D) Patient 1 comparison of PPM-optimized and clinical methotrexate regimen. (E) Patient 2 comparison of PPM-optimized and clinical absolute neutrophil count. (F) Patient 2 comparison of PPM-optimized and clinical platelet levels. (G) Patient 2 comparison of PPM-optimized and clinical 6MP dosing regimen. (H) Patient 2 comparison of PPM-optimized and clinical methotrexate regimen.

1.3.4 Drug Interaction Mapping

Drug interaction mapping was conducted to visually correlated drug dosing with target platelet and ANC levels. The substantial variations in drug interactions and resulting outputs between the patients are clear indicators of the need to personalize and continuously optimize treatment. For both patients, 6MP and methotrexate were correlated with ANC output, with the maps clearly showing a clear difference in drug interaction behavior between patients 1 and 2 (Figs. 1-5). This was a demonstration of the importance of personalizing care in ALL. For patient 1, a broad range of 6MP doses was capable of maintaining the patient within the ANC target range. A narrower range of methotrexate doses resided within the ANC target (Fig. 5A). The methotrexate dosing spectrum exhibited a clear dose-dependent fluctuation from the ANC target range at the lower and higher dosing domains, further demonstrating the importance of pinpointing the right patient-specific doses. For patient 2, a narrow range of doses for both 6MP and methotrexate were required to maintain the ANC target range (Fig. 1-5).

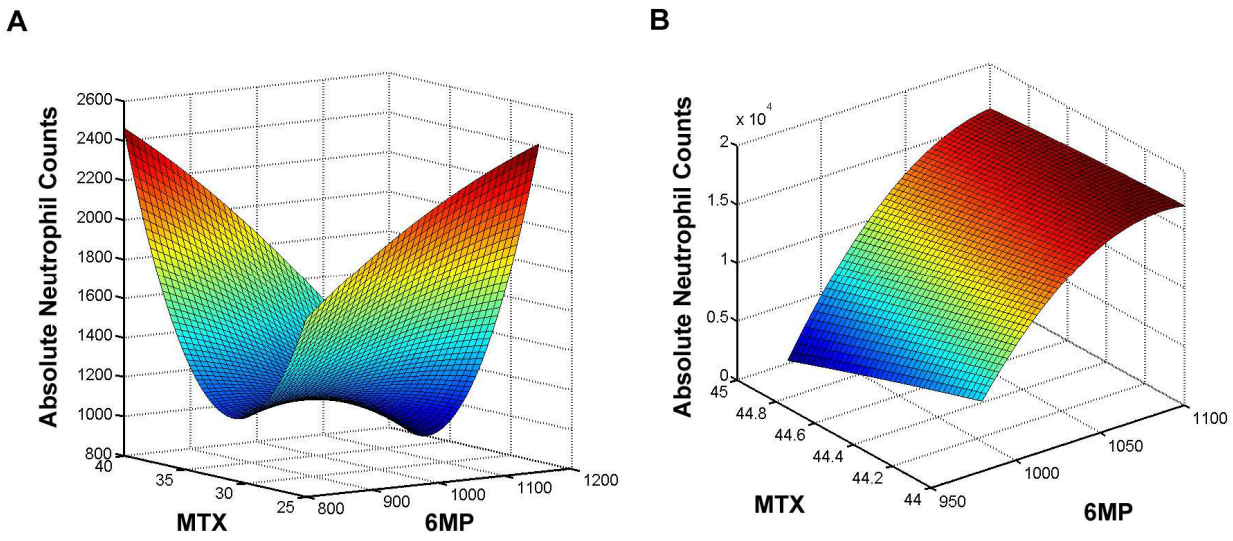

Figure 1-5. Phenotypic mapping correlating 6MP-methotrexate interactions with absolute neutrophil counts. (A) Patient 1 mapping is shown. (B) Patient 2 mapping is shown.

1.3.5 Drug Interaction Analysis

Quantitative drug interaction analysis was conducted to assess the contribution of first order terms (FOT), drug-drug interaction terms (ITA), and second order terms (SOT) towards patient treatment outcomes. Patient 1 interaction analysis was plotted for clinician-guided therapy (Fig. 1-6) and PPM-optimized therapy (Fig. 1-7). When ANC levels deviated from the target range substantially on day 85 (Fig. 1-6), a noticeable reduction was observed in the drug interaction term (ITA), demonstrating the importance of maintaining the ITA at a threshold that maintains target ANC levels (Fig. 1-7)

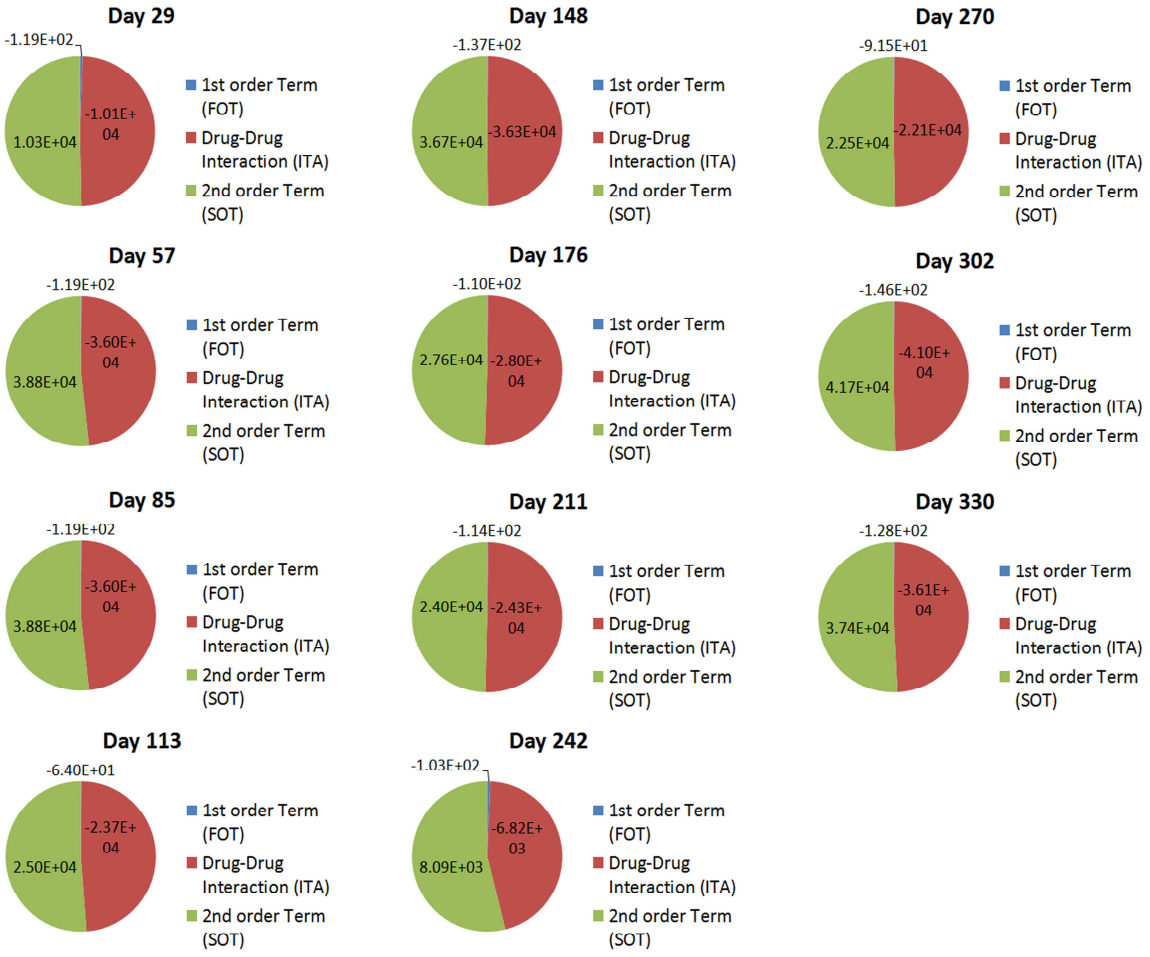

Figure 1-6. ITA, FOT, and SOT contributions towards clinically-observed treatment outcomes for Patient 1.

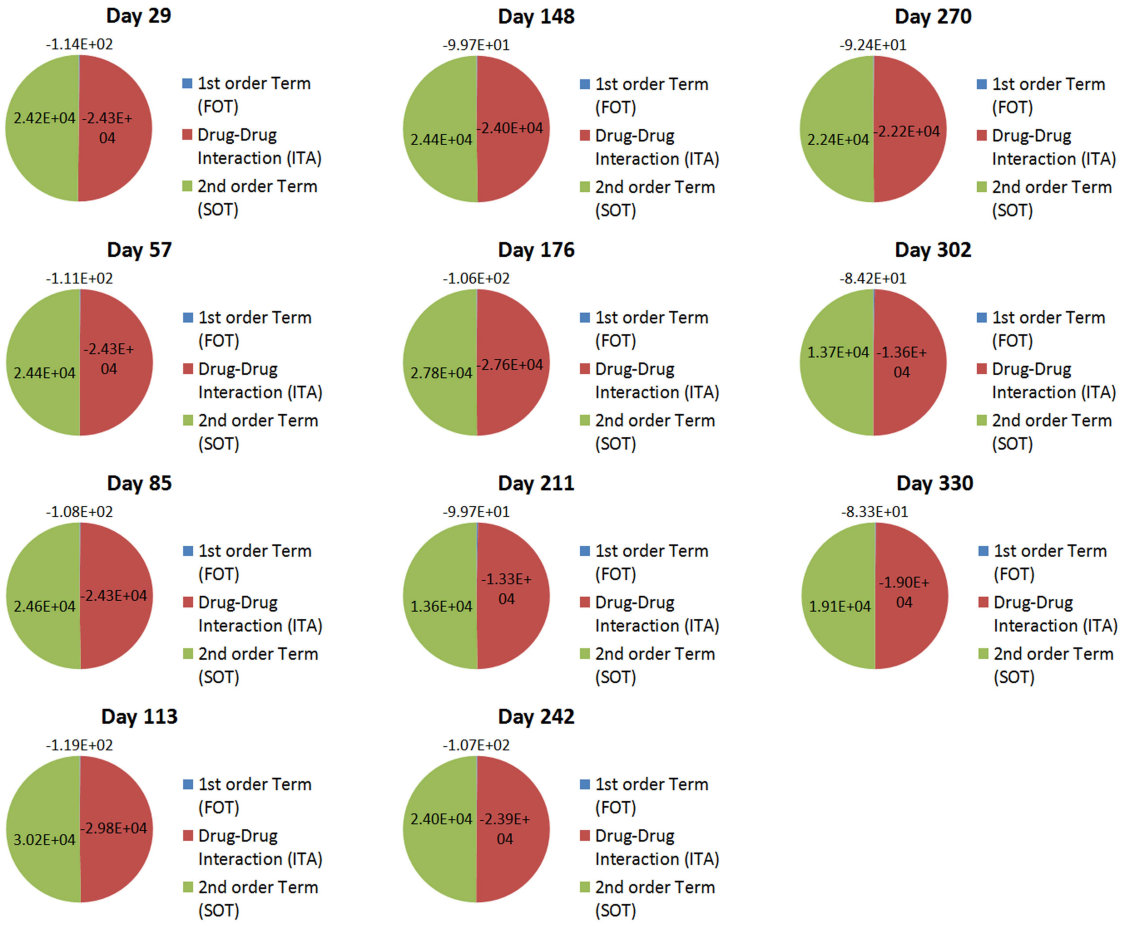

Figure 1-7. ITA, FOT, and SOT contributions towards PPM-optimized treatment outcomes for Patient 1.

For patient 2, a reduction in ITA from days 148-176 was observed that correlated with a substantial deviation from the target ANC range under clinician-guided therapy (Fig. 1-8). This deviation was notably absent in PPM-guided interaction mapping (Fig. 1-9). This further indicates the importance of maintaining a threshold ITA value in order to maintain target ANC levels.

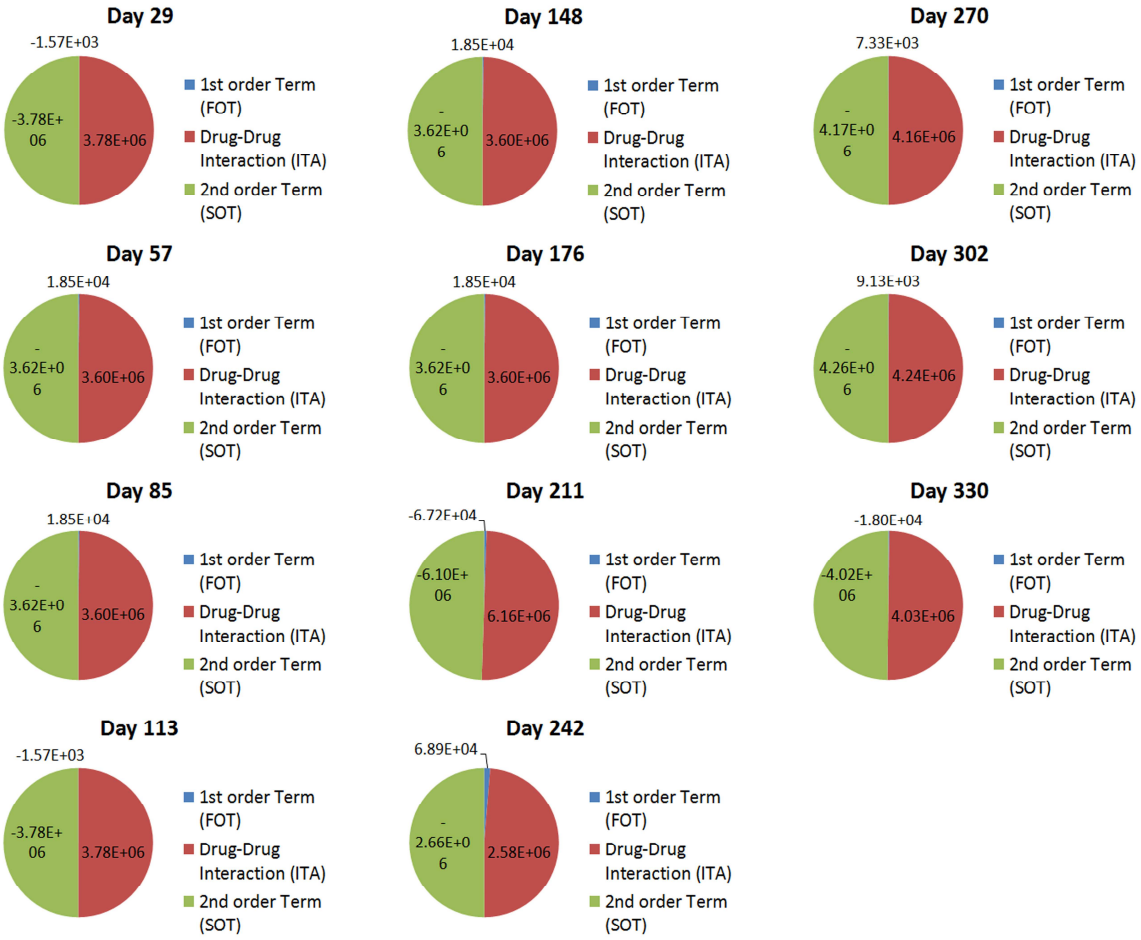

Figure 1-8. ITA, FOT, and SOT contributions towards clinically-observed treatment outcomes for Patient 2.

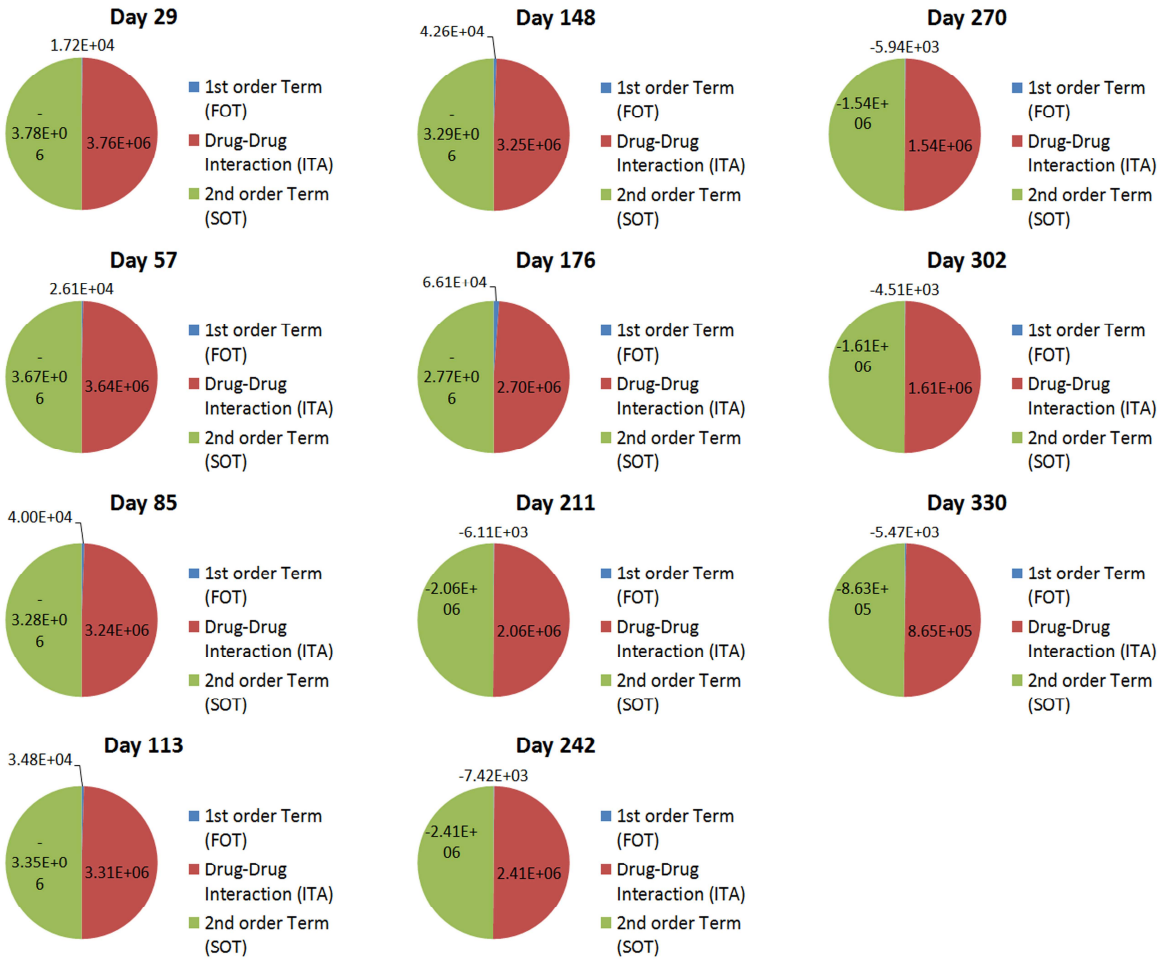

Figure 1-9. ITA, FOT, and SOT contributions towards PPM-optimized treatment outcomes are shown for Patient 2.

1.3.6 The Impact of Parabolic Medicine on Optimized Drug Development and Personalized Therapy

The clinical management of combination therapy is challenging, given the infinite dosing space in which patient-specific drug administration parameters reside. This further confounds the identification of these parameters since patient physiology changes over time as new drug regimens are introduced to address co-morbidities, or additional procedures are administered

(e.g. bone marrow transplants). These factors have made the optimization of patient-specific combination therapy, at a specific timepoint, or during the entire course of care, virtually impossible.

The inability, until now, to pinpoint drug-dose ratios in combination therapy is a problem that spans both drug development and individualized care. In the context of drug development, this is due to the fact that optimized dosing parameters can also exist on a universal, or population-based scale. This makes population-optimized combination therapy possible. However, current drug development strategies preclude the design of population-optimized therapy. More specifically, current combination therapy strategies use high throughput screening to identify lead compounds. These compounds are then evaluated further to assess efficacy and safety. Designing combination therapies or monotherapies subsequently involves dose escalation towards maximum tolerated dose (MTD)-based additivity. In addition, drug synergy-based prediction serves as a conventional strategy to further enhance treatment outcomes. However, the study reported here as well as others based on PPM demonstrate that pinpointing drug dose can have a profound impact on drug synergy and antagonism, and that dosing outside of optimal ranges can render combinations that were predicted to be synergistic, ineffective. At the same time, less effective or ineffective combinations can be rendered maximally efficacious through drug-dose optimization. Dose escalation and prediction-based design, therefore implicitly preclude the optimization of drug-dose ratios and identification of the best therapeutic formulations. This is a major driver of the exorbitant costs and high failure rates of drug development. Therefore, PPM demonstrates that drug-dose profoundly impacts drug selection, and that both must be optimized simultaneously to optimize therapeutic efficacy and safety in the clinic.

As this study and others demonstrate, PPM eliminates the use of brute force to assess both the dosing and drug selection space. By substantially reducing bias during the initial drug development process, we can interrogate the entire drug-dose and selection space to rapidly optimize both attributes that will mediate maximal efficacy and safety. To overcome the burden of sub-optimal dosing and combinatorial drug selection, PPM re-optimizes at each stage of development, where in vitro optimization refines the list of lead drug combination candidates. Drug-dose ratios and drug selection are re-optimized at the preclinical stages, and as this study shows, in-patient optimization can be realized as well. In lieu of brute force screening, parabolic medicine substantially accelerates these processes. Population and personalized optimization collectively provide powerful information into drug-dose ratios that enable dramatic increases in efficacy and safety. The implicit validation of these combinations during optimization and re-optimization has already made major strides towards improving clinical outcomes over conventional standards with dramatically accelerated developmental timelines.

In the context of personalizing patient regimens, conventional approaches have included dosing algorithms, pharmacogenomics, pharmacokinetic modeling, and other strategies. [17-18] However, due to substantial changes in patient physiology that are inevitable encountered during treatment from regimen changes (e.g. changes in drug dose, formulation from intravenous to oral administration, etc.) and other procedures (e.g. bone marrow transplant, etc.), dynamically optimized care that is not enabled by these aforementioned modalities is required. To overcome this challenge, PPM correlates patient response to therapy in a parabolic fashion that pinpoints, at all times, the best possible combination therapy regimen. PPM patient-specific dosing PPM is particularly effective at co-optimization of combination chemotherapy and simultaneous immunosuppression following bone marrow transplantation as it is not limited by the number of

drug inputs. This ability to calibrate optimized and patient-specific regimens makes PPM broadly applicable towards oncologic, infectious disease, cardiovascular, wound healing, neurological, and a broad spectrum of other indications.

1.4 Conclusion

Maintenance therapy for ALL administers standardized regimens of dexamethasone, vincristine, 6MP, and methotrexate in an effort to maintain treatment efficacy as well as target ANC and platelet levels. Using conventional titration, ANC levels often fluctuate outside of the target range, and can result in treatment complications. Furthermore, eliminating these fluctuations can often be achieved using drug dosages that are substantially lower than those given in conventional clinical practice. This opens the doors to possibly reducing acute or long-term side effects due to the duration of maintenance therapy. Towards this objective, this study used PPM to retrospectively optimize combination therapy regimens by modulating all 4 drugs, or 6MP and methotrexate (clinical practice). While this was achieved using clinical data that had already been collected, prospective PPM can achieve profoundly improved patient outcomes based on the acquisition of a modest level of increased serum analysis compared to conventional clinical protocols. Therefore, when the prospective clinical procedure is readily adapted to PPM-based treatment optimization, obtaining the right data will redefine the way that patients are treated, forging a path towards substantially improving durable response rates.

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