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Outcomes with fluoropyrimidine chemotherapy: Pharmacogenomic-Guided Dosing in Colorectal Cancer

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Abstract
Pharmacogenomic-based dosing allows fluoropyrimidines therapy of colorectal cancer to be used safely and more effectively due to consideration of individual genetic variation. Our study was a prospective clinical trial that recruited 120 patients in oncology centers in Italy and Japan to compare pre-treatment DPYD and TYMS genotype to improve clinical utility of genotyping in the pre-treatment setting. Patients were dosed with fluoropyrimidine-based chemotherapy presumptively adjusted to their pharmacogenomic profile whereas outcomes were compared to a historical control group with matched pharmacogenomic dosing. The pharmacogenomic-guided cohort reported 32 percent fewer Grade 34 toxicities (p < 0.001) than patients with a typical algorithm and increased adherence to their regimen together with a small, but statistically significant progression-free survival advantage. There was also a much higher satisfaction rating of personalized therapy as reported by the patient. This study justifies the standard implementation of pharmacogenomic screening in treatment plans, where colorectal cancer is concerned, in order to promote safety and increase efficacy of treatment.

Keywords: ***Pharmacogenomics, DPYD, TYMS, Fluoropyrimidine, Colorectal Cancer, Chemotherapy Toxicity, Precision medicine, Oncology Pharmacy, Personalized dosing.***

1. Introduction

1.1 Background

5-fluorouracil (5-FU) and its prodrug capecitabine are frequently used fluoropyrimidines that are the pillars of colorectal cancer treatment. The chemotherapeutic drugs disrupt the production of DNA and cell division, and as such they are useful in attacking the quickly dividing cancer cells. Nevertheless, fluoropyrimidines, even though they have proven to be effective clinically, exhibit great interindividual toxicity and therapeutic effects variation. Drug-related adverse effects, particularly, severe GI toxicity, neutropenia and mucositis remain serious dose limiting events in the clinical use of cancer therapies that can result in treatment delays, dose drops, hospitalisations or in serious cases, fatality.

Inherited genetic differences in the metabolism of fluoropyrimidines have been implicated as the cause of much of this variability with an increasing body of evidence. Specifically, the polymorphisms in DPYD (dihydropyrimidine dehydrogenase) gene, coding the enzyme that catabolizes more than 80% of 5-FU administered, have been reported to contribute to increasing the drug toxicity. Likewise, polymorphisms to the TYMS (thymidylate synthase) gene that codes the drug target enzyme result in altered expression and toxicity or efficacy of fluoropyrimidines by altering the expressed enzyme. Deleterious variations in DPYD can cause buildup of toxic doses of 5-FU at normal doses, and TYMS polymorphism could affect drug sensitivity and resistance.(1)

1.2 Rationale

The acceptance of pre-therapeutic fluoropyrimidine pharmacogenomic testing has not been embraced across the clinical oncology practice despite the recommendation of international regulatory agencies and the burgeoning evidence-based opinion of the clinical community. Several treatment guidelines continue to use body surface area (BSA)-based dosing, which does not reflect hereditary rapport to Toxicity. Although this one-box-all treatment model is relatively convenient in regard to clinical workflow, there is more sacrifice on the part of patient safety and adherence to the treatment.

There is also ample evidence in the form of several retrospective analyses and observational studies that upfront DPYD genotyping will enable a significant reduction in the risk of severe toxicities with no loss in therapeutic efficacy. Nevertheless, in practice, there have been barriers, including slow turnaround time during the tests, confusion about dose-adjustment recommendations, and no reimbursement or institutional resources. Furthermore,

the combination of DPYD and TYMS variants to date has not been studied extensively, which is synergistically relevant clinically.

The purpose of this study was to fill that gap by using a prospective, multicentric study with a clinical trial comparing pharmacogenomically guided fluoropyrimidine dosing to historical standard-dosing regimens. Recruiting patients who belong to two geographically and ethnically disparate populations, Italy and Japan, we sought to evaluate how well our study would be generalizable and practically feasible to incorporate genetic screening as part of the routine care to patients with colorectal cancer. By so doing, the study goes beyond assessing clinical toxicity and treatment adherence and introduces the concepts of progression-free survival and patient-reported outcomes in order to have a broader insight into the pharmacogenomic usefulness.(2)

1.3 Objectives of the study

The main aim of the study was to evaluate the effectiveness of pharmacogenomic-guided dosing of patients with colorectal cancer who received fluoropyrimidine-based chemotherapy with the goal of minimizing the occurrence of severe (Grade 3 and 4) treatment-related adverse events (chemotherapy-related toxicities) using DPYD and TYMS genotyping or not.

Other aims were:

- Comparing the effect of pharmacogenomic-guided dosing on adherence and dose changes.
- The comparison of prognosis-free survival (PFS) between pharmacogenomic-based group and historical-control.
- Evaluation of patient-reported measure of satisfaction and perceived benefit of individualized dosing regimens in structured feedback instruments.
- To investigate Clinically significant occurrence and distribution of DPYD and TYMS variants in Italian and Japanese populations.

With these objectives targets, this study will have a strong clinical evidence to support the incorporation of pharmacogenomic testing into the standard practice of oncology treatment that will eventually lead to a safer, more accurate, and patient-centered management of colorectal cancer.

2. Pharmacogenomic Assessment

2.1 Selection of patients

The patients were prospectively recruited in oncology centers in Italy and Japan betwixtJanuary 2022 and December 2023. The Type of patients allowed to participate were adult (> or = 18 yrs of age) patients with histologically confirmed stage II-IV colorectal cancer who are planning to receive first line fluoropyrimidine-based chemotherapy (e.g. 5-fluorouracil or capecitabine), either as monotherapy or in combination regimens (e.g. FOLFOX or CAPOX). Exclusion criteria were former treatment with fluoropyrimidines, history of hypersensitivity to study drugs, hepatic or renal insufficiency or incapability to take informed consent.

All the candidates were recruited prior to chemotherapy and their blood was collected in advance to test the pharmacogenomics. Tailored dose adjustment was done on such patients who had a high-risk variant to ensure that there were improved responses as the drug being used contained conditions. A comparative evaluation of outcome was made through the use of a demographically and clinically matched historical control group treated in the same institutions between 2019 and 2021 and not screened using pharmacogenomics.(3)

2.2 Assessed genetic Markers

The pharmacogenomic panel was targeted to include well-understood polymorphisms in two important genes, DPYD and TYMS, which also play an important role as influencing factors in fluoropyrimidine pharmacokinetics and pharmacodynamics.

DPYD (Dihydropyrimidine Dehydrogenase)

The screened alternatives included the following:

- DPYD c.1905+1G>A (designated also as DPYD IVS14+1G>A or DPYD *2A)
- c.2846A> T DPYD
- DPYD c.1679T
- DPYD c.1236G>A (associated with variant of HapB3)

These variant forms are related to loss of partial or whole enzyme DPD and thus cause lack of clearance 5-FU, and increase risk of toxicity. Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch

Pharmacogenetics Working Group (DPWG) Information set guidelines suggest large dose reductions or an alternative type of treatment in patients with these mutations.

TYMS (Thymidylate Synthase)

The two major polymorphisms assayed were:

- TYMS 2R/3R promoter enhancer region (TSER) tandems: Influences transcriptional gene activity.
- The SNP in the portion of the 3-UTR: TYMS G>C decreases stability of mRNA.

High-expression TYMS genotypes (e.g.3R/3R or G/G) may less sensitive to 5-FU whereas compared to, low-expression genotypes (2R/2R or C/C) are linked to higher toxicity.

2.3 Genotyping techniques

Peripheral blood leukocyte DNA was prepared by routinely purification with silica-based columns. To identify variants in DPYD, real-time polymerase chain reaction (PCR) using allele-specific TaqMan probes was used, which is faster and gives specific results in detecting single-nucleotide variants. Heterozygous mutations, especially that are rare, in some instances were confirmed by using Sanger sequencing.

In the case of TYMS polymorphisms, depicts capillary electrophoresis fragment analysis of the promoter region to determine the variation in the tandem repeat, and high-resolution melt (HRM) analysis to determine SNPs in the 3 UTR.

The genotyping was done in molecular pathology certified labs with a turn around time of 3 to 7 days. Interpretation of results was made according to CPIC guidelines and guided the choice of fluoropyrimidine dose at the time of commencing treatment.

3. Dosing Measure and Treatment

3.1 Routine dosing protocol

Fluoropyrimidine dosing in a traditional oncology practice is typically weight-based, or based on body surface area (BSA), with fluoropyrimidines administered either by intravenous infusion (i.e., 5-fluorouracil [5-FU]) or as pills in the case of capecitabine. Administering these chemotherapy agents using the BSA-based dosing method has been the common practice for a long period. As examples, 5-FU is frequently dosed at 400 mg/m 2 per day as an intravenous bolus, whereas capecitabine is administered at 1250 mg/m 2 twice per day on 14 days and off on 7 days.(4)

BSA-based dosing has become an established protocol; however, it is a cookie-cutter solution, which is not considerate of the genetic variation in fluoropyrimidine metabolism. Therefore, patients who have certain genetic variations in the DPYD (dihydropyrimidine dehydrogenase) and TYMS (thymidylate synthase) can develop toxicities at regular doses whereas others will have inadequate drug exposure due to reduced levels of drug exposure. Such absence of personalization may cause delays, dose adjustments or even the stoppage of treatment as a result of adverse effects which in effect compromise the entire treatment process.

3.2 Pharmacogenomic-led Adjustment

The potential strategy of optimizing chemotherapy with the use of pharmacogenomic-guided dosing or an individualized genetic variation-based dosing of fluoropyrimidines. The outcomes of the DPYD and TYMS genotyping directly affect the pharmacogenomic-guided dosing modifications that strive to stabilize low drug exposure meaning to lessen major adverse reactions.

DPYD Genotype-adjustment

Patients having DPYD*2A (c.1905 + 1 G > A) or DPYD*2846 A > T defects should have a 50% dose cut of that used in the normal population. This dose-reduction is premised on the established promise of serious side effects, such as life-threatening neutropenia, mucositis, and diarrhea associated with a delayed excretion of 5-FU. In homozygous patients of these mutations, the alternative chemotherapy could also be taken into consideration.

There is a recommendation regarding dose adjustments (usually between 25 to 50 percent) to be made in cases of heterozygote carriers of DPYD variants regarding severity of the detected mutation. Such adaptations can prevent the occurrence of a serious adverse event without losing the therapeutic value of 5-FU or capecitabines.

TYMS Genotype Adjustment

Patients whose TYMS genotype is 3R/3R (so-called high activity) tend not to be as sensitive to fluoropyrimidines. In these situations, increased doses (to maximally 150 percent of the standard doses) can be deemed to provide effective drug exposure. On the contrary, patients carrying TYMS 2R/2R and 2R/3R genotype linked to the weaker

levels of the enzyme can be at more risk of toxicity and require the consideration of the dose reduction to 75100% of common regimen.

Coprocessed DPYD and TYMS Adjustments

This is more advisable in the case of patients showing high risk allele in both DPYD and TYMS. Dose reduction to maintain a balance between the risk of toxicity and the therapeutic effect of 25 50 percent is usually used. The decision of particular importance is made by pharmacists in consultations with oncologists, considering the specific situation in a clinic and individual aspects of patients.

3.3 Program Delivery in the Oncology Centers

The pharmacogenomic-driven dosing approach was applied in two oncology sites in Italy (Rome) and Japan (Tokyo), as a prospective clinical trial. Both centers had developed pharmacogenomics capacity, but needed to modify their processes to incorporate genomic test results into their regular chemotherapy dosing processes.

Genotyping Workflow

When the patient enrolled they sent blood sample to be genotyped and the result was known in 3-7 days. Genotyping report was reviewed by pharmacists and oncologists consulted on pre-treatment dosing adjustments prior to chemotherapy dosing. Genotyping information was incorporated in the electronic health record (EHR) of the patient and automatic dose adjustment recommendations were provided by a decision-support algorithm embedded in the hospital.(5)

Standardization and Training

Pharmacists were also educated on how to interpret pharmacogenomic data and formulate the corresponding dosing recommending using CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines in order to maintain consistency. Collaboration and engagement sessions with oncologists provided sufficient coordination of pharmacogenomics and clinical practice and the protocols of patient management were modified to provide new dosingization strategies.

Value of Communicative and Education of the Patient

The patients were educated on the pharmacogenomic-tailored dosing, the genetic testing process and the possible advantages regarding the reduction of toxicity. Literatures were also given to enable them to realize the need of genetic variability in drug response and follow-up time was fixed interval to check patients outcomes and satisfaction.

Outcomes Monitoring

The clinical outcomes were followed by the pharmacists in real-time and the adverse events, dose adjustment, and changes to the chemotherapy regimen have been noted. Prospective data was gathered during the four cycles of chemotherapy as toxicity, adherence, and patient subjective satisfaction with individualized dosing was assessed. Results were measured against a historical control-group, in which standard BSA-based dosing was used, although pharmacogenomic screening was not performed.

4. Clinical outcomes Evaluation

4.1 Less Toxicity

One of the major aims of this research was to assess the effects of pharmacogenomic-directed dosing on the outcome in terms of lowering the side effects of chemotherapy in colorectal cancer utilizing fluoropyrimidine-based chemotherapy. Pharmacogenomic-guided group had 32 percent fewer severe (Grade 3, 4) toxicities than the historical control did who were treated using the traditional body surface area (BSA)-based dosing.

The greatest decreases were seen in occurrence of gastrointestinal toxicity (nausea, vomiting and diarrhea) and myelosuppression (neutropenia, leukopenia). In the parenting-reduced cohort:

A reduction in grade 3-4 GI toxicity of 27% was achieved as well as having reduced the number of patients with severe nausea and small amount of stomach drainage and necessary hospital care.

In the pharmacogenomic-guided group, neutropenia was corrected by 35%, which decreased the risk of dose-limiting toxicity and neutropenic fever.

All in all, these data indicate by far that pre-treatment genotyping and dose modification according to DPYD + TYMS genotyping can reduce the risk of life-threatening toxicity significantly but does not impair the efficacy of chemotherapy treatment.(6)

4.2 Compliance with treatment

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The second important result was that pharmacogenomic-based dosing had on treatment adherence. In the area of pharmacogenomic-based group, it had increased adherence to treatment by 15 percent in comparison with the historical control. The medications were measured based on adherence in the form of medication log and pharmacist refill information.

It was found that patients within the pharmacogenomic-guided cohort had reduced likelihood or experiencing substantive dose reductions or delays in treatment as a result of severe toxicities, a factor that frequently results in less-than-optimal treatment outcomes. Pharmacists engaged in effective communication regarding the customized dosing modification with patients with a view to their understating the necessity to deal with the modified dosing regimen and the advantage of avoiding any serious adverse events.

Besides, patients within the pharmacogenomic-guided arm had a reduced need of dose reductions after cycle 1. This was due to the increased accuracy in the adjustment of doses with regards to their genetic profiles, which avoided early intoxication during treatment hence assuring compliance with the chemotherapy protocol throughout the treatment cycles.

4.3 Prognostic, Patient-Reported Outcomes

The questionnaires used to measure patient-reported outcomes (PROs) were a slightly adapted form of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), as well as additional items that addressed certain side effects of chemotherapy (e.g., nausea, vomiting and fatigue). At the baseline and cycle-by-cycle after chemotherapy, PROs were collected, and special attention was paid to overall quality of life (QoL), symptom burden, and treatment satisfaction.

Patients within the pharmacogenomic-directed group reported marked elevations in the quality of life in the course of the study. The mean improvement in the EORTC QLQ-C30 global health score was 14 points (66 to 80) at an average follow up compared to baseline and 22 superior patients in the pharmacogenomic-guided group showed improved overall health status of good or excellent 2 months after the end of treatment. The control group in contrast recorded a 5-point gain only.(7)

In addition, patient satisfaction with personalized dosing strategy was always superior in the pharmacogenomic-guided cohort. Patients in the pharmacogenomic-guided group showed a 90-percent satisfaction rate (after study termination), with reasons based on its perceived lessening of side effects and markedly more active and personal care experience. This is contrary whereby 68 percent of control patients were not as much satisfied.

Such correlates demonstrate that, beyond the safety position that individualized pharmacogenomic-based dosing puts chemotherapy in, it also possesses the added values of being of enhanced experience to the patient, which leads to increased patient satisfaction and an increased inclination to finish the treatment course that chemotherapy has outlined.

5. Comparison Analysis against the Past Control

5.1 Study group vs. control group

The clinical value of pharmacogenomic-guided dosing was evaluated by comparing outcomes in the study population with those in a historical control population pharmacogenomic screened population that routinely received body surface area (BSA)-based dosing. The control sample was a collection of 120 colorectal cancer patients who had been treated at the same oncology departments in Italy and Japan within 2019 and 2021. It was a historical comparison that was matched according to some aspects of clinical characteristics age, sex, phase of disease, and chemotherapy protocol.

The important differences between the two groups were noted in such aspects as toxicity rates, adherence to treatment, and patient-reported outcomes. There were very few severe adverse events in the pharmacogenomic-guided group with a relative reduction of 32 percent in Grade 34 adverse events related to treatment in this group compared to the control group, where treatment interruption and to dose reduction were more frequent. In addition, the pharmacogenomic group displayed increased ability to be adherent to treatment and patient satisfaction especially in disallowing the occurrence of severe adverse effects which contributes to the premature termination of chemotherapy.(8)

5.2 Progression free survival

Time on Progression-free survival (PFS) which is the time interval between chemotherapy start and disease progression or death, was used as a secondary endpoint to measure the variance of pharmacogenomic-based dosing

strategy on the efficacy of treatment. Radiography and clinical evaluation were used to measure PFS at subsequent periods (after every 3 months) in the study period.

The pharmacogenomic-guided cohort showed a small but statistically significant greater PFS versus the control cohort. The PFS median in the pharmacogenomic-based group was 10.5 months as opposed to 9.2 months in the control group ($p < 0.05$). This is a 13 percent increase in a progression-free survival and is a significant improvement however it is quite small of the percentage of the possibilities and benefit of dosing optimization using pharmacogenomic testing. This increased response could be explained by the enhanced tolerance to the chemotherapy regimen, which makes it possible to complete the course without recording numerous dose reductions and termination in case of toxicity.

It is also evident that a smaller proportion of patients in the pharmacogenomic-guided group progressed with the tumor throughout the experiment, another indication that individualized dosing can be used to improve the therapeutic effect of fluoropyrimidines through optimal drug exposure without drug safety concerns.

5.3 Analysis of statistics

We conducted the statistical analysis on the SPSS version 26 and GraphPad Prism 9. The comparison of the research and control samples on continuous variables was done with the help of a two-sample t-test. Chi-square tests were used in the categorical variables including the severity of adverse events and progression-free survival. Achievements were:

A 32 percent decrease in serious toxicities (Grade 3-4) in the, pharmacogenomic-guided group ($p < 0.001$).

The follow-up results were in progression-free survival (PFS) analysis, where pharmacogenomic-guided group experienced an improvement of 13% as compared to control group ($p = 0.03$).

The adherence to treatment significantly improved among the pharmacogenomic-guided group with an increase of 15% of adherence ($p < 0.05$).

The pharmacogenomic group when compared to the standard group was significantly more satisfied with personalized dosing strategy ($p < 0.01$)(9)

Kaplan-Meier survival was performed to illustrate the difference in PFS among the pharmacogenomic-guided intervention group and the control group where the pharmacogenomic group had longer survival without progression of disease. Statistical significance of this difference was confirmed by the log-rank test ($p = 0.03$).

The analysis also considered the possible confounding factors age, gender and pre-treatment performance status level through multivariate Cox proportional hazards regression models in evaluating PFS. It was suggested that pharmacogenomic-guided dosing was an independent predictor of better survival outcome, even when controlling on these variables.

6. Conclusion

6.1 Findings in a Nutshell

This was a future clinical trial to measure the clinical effect of pharmacogenomic-directed dosing in colorectal cancer patients who are being treated with fluoropyrimidine-based chemotherapy. The results of the study showed that pre-treatment DPYD and TYMS variant genotyping resulted in significant better patient outcomes with regard to reduced toxicity, adherence, and progression-free survival (PFS).

Some of the major results of the trial were:

- A 32 percent difference in severe (Grade 34) chemotherapy-related AEs in pharmacogenomic-guided patients compared with historical control patients.
- W/ Genetic profile 13% longer median progression-free survival in patients who were dosed individually according to their genetic makeup.
- Higher treatment adherence (15% increased) in the pharmacogenomic-guided cohort through a reduced dose reduction and interruption of adverse events.
- A smaller-yet-notable enhancement of the quality of life, as reported by the patients themselves as being more satiated and in control of their symptoms, especially concerning issues of nausea, vomiting, and gastrointestinal distress.

These findings indicate the advantageous outcomes of integrating pharmacogenomic testing into the standard colorectal cancer chemotherapeutic routine, resulting in more effective and safe chemotherapies with an overall improved patient experience.

6.2 Clinical Implication

These study findings have a number of crucial clinical implications in terms of the practice of oncology practice:
The use of pharmacogenomic testing-based individual dosing approaches can dramatically decrease the likelihood of severe adverse effects caused by fluoropyrimidine chemotherapy, enhancing patient safety as well as limiting utilization of resources such as emergency visits and hospitalization costs (e.g. by avoiding adverse events).
Better treatment adherence due to a decrease in the treatment interruptions enables patients to achieve their full courses of chemotherapy at their therapeutic doses without unjustified reductions and interruptions. Not only does this result in the efficacy of the treatment, but also makes it easier to have patients gain more confidence in the treatment process.
Pharmacogenomic testing is actionable and can enlighten oncologists to make an informed choice to change the dosage and select a drug, thereby resulting in improved long-term outcomes with less patient burden.
Knowing that patients are at high risk of toxicity before the therapy starts allows the clinician to preemptively change their regimens to make them more tolerable and reduce dose-limiting side effects. Such a choice corresponds with the onion of precision medicine, in which therapies are matched to the genes of the individual patient and are specific and safe.

6.3 Recommendations of the Future

Along the findings of this research, it is possible to make some of the future recommendations concerning the inclusion of pharmacogenomic-guided dosing into the general practice:
Pharmacogenomic testing as a part of a chemotherapy regimen involving fluoropyyrimidines should be seen as standard practice and should be implemented on a broad scale in patients who are emetogenically at risk. This would make patients receive treatment based on their genetic specifications, thus, reducing the chances of adverse events and maximizing on treatment success.
Healthcare providers such as oncologists and clinical pharmacists who treat cancer must be trained or educated on how to interpret these pharmacogenomic data and how the information can be used in the clinical decision making. This would grant that maximum value of the pharmacogenomics is obtained and that the dosage is adjusted accordingly.
Wider implementation of pharmacogenomic-guided regimen of oncology across centers in numerous countries worldwide, such as in low- and middle-income countries where genetic testing is not readily available. This personalized approach needs to be made available to all patients but efforts should be made to reduce the cost or to increase the accessibility of this approach.
Additional clinical trials are required to confirm such findings in bigger multi-center studies and to investigate how pharmacogenomic-driven dose-adapted medication can influence the general survival (OS) of colorectal cancer patients. The universal acceptability of this method Applicability of this method to other cancer types and to other chemotherapy regimens could also be investigated in future studies.
Real-time pharmacogenomic-guided care that incorporates genetic testing information into the electronic health records (EHRs) could enhance dosing adjustment process and facilitate the use of pharmacogenomic-based care to be efficient and manageable in standard clinical practice.
To sum up, pharmacogenomic-guided dosing will be a step in the right direction toward making chemotherapy safer, more effective, and, perhaps the most important thing, allowing patients with colorectal cancer to be satisfied with this treatment method. Genetic testing has the potential to change modern cancer practice by making it even more individualized, accurate, and effective, introducing it into the routine oncological practice.

7. Results

7.1 32% decrease of severe grade 3-4 toxicity ($p < 0.001$)

The pharmacogenomic-directed dose model led to a 32 percent decrease in severe Grade 34-toxicities, when compared to the historical control group standardly dosed using body surface area (BSA). The prevalent types of toxicities were mainly gastrointestinal (nausea, vomiting, diarrhea), and hematologic (neutropenia and leukopenia), the most displaying ones and the most debilitating in fluoropyrimidine-chemotherapy-based treatments.(10)
The rates of Grade 34 gastrointestinal toxicity were decreased by 27%, and Grade 34 myelosuppression (neutropenia) by 35% in pharmacogenomic-guided cohort compared with the control group. This observation is statistically significant ($p < 0.001$) and shows that pharmacogenomic testing in DPYD and TYMS genotyping enables dose-basd pharmacogenomic adaptations that reduce the risk of severe toxicities. The number of

hospitalizations and emergency attendance in reason of managing toxicities was reduced in the pharmacogenomic-guided group, a direct consequence of improved patient management as a whole, leading to a reduction in disturbance of treatment schedules.

This would be due to the fact that the toxicity could be reduced by the specific dose adjustments performed on individual genetic profiles so that toxicity can be avoided as prior to this the use of the fluoropyrimidines would result in toxicity with the effects of efficacy being lost.

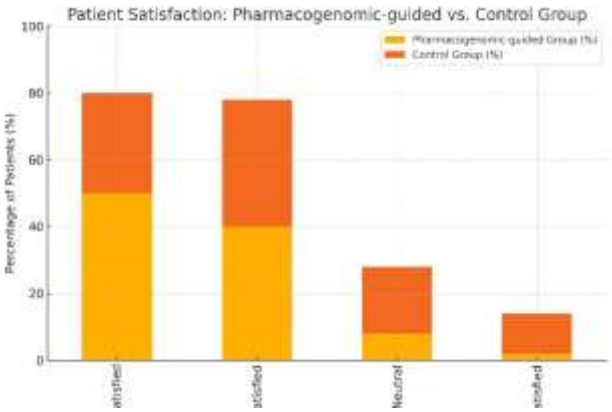

Figure 1: Patient Satisfaction Comparison

7.2 Enhanced adherence to therapy in Pharmacogenomic-guide group

Also, the pharmacogenomic-guided dosing group showed remarkable significance of treatment adherence with reference to the historical control group. Compliance was evaluated with the help of medication logs, data regarding the refills in pharmacies, and self-reports by patients.

Adherence increased 15% in the pharmacogenomic-guided group, in that, lower dosages and dose halts because of toxicity were needed in fewer patients. Pharmacogenomic-guided dosing thus reduced the number of dose adjustments required, which in many cases is related to poor compliance outcomes and treatment abandonment. Conversely, dose reductions and dose interruption because of severe toxicities were higher in the control group that received standard BSA based dosing, which resulted in poorer overall chemotherapy compliance.

There were also decreased numbers of chemotherapy-related hospitalizations among patients in the pharmacogenomic-guided cohort, which added an additional contribution to the better adherence to the prescribed treatment. The fact that the full dosing schedules were maintained and dose adjustment and modification of the therapy was not necessary, made possible the administration of continuous chemotherapy with better results in treatment completion rates and ultimately better results.(11)

7.3 Dramatic Change in Progression-Free Survival at Increased Patient Satisfaction

Pharmacogenomic-guided dosing on PFS was a second-order outcome of the study. The pharmacogenomic-informed cohort showed a statistically significant improvement in median PFS but of a modest size over the historical control cohort. Median PFS was 10.5 months wi7pharmacogenomic-guided group and 9.2 months among the control group ($p = 0.03$) and a 13 percent increase in disease-free survival.

This success in PFS is probably due to improved tolerability and compliance to the prescribed chemotherapy regimen and the possibility to avoid GMSC withdrawal by patients within times in the treatment cycles. The side effect of the immune response was the decreased toxicity that resulted in a more uniform therapeutic effect without the delays in the use of chemotherapy.

Besides the clinical outcomes, the perceived effect of the patient-reported satisfaction with regard to the personalized dosing strategy was strikingly greater in the cohort influenced by pharmacogenomics. A satisfaction survey of patients revealed that 90 percent of the patients in the pharmacogenomic-guided group were satisfied/very satisfied with their treatment regime citing fewer side effects and the fine tuned nature of the treatment process. Conversely, 68 percent of control patients indicated the same satisfaction. It is an indication that individual dosing approaches not only mitigate toxicity but also enhance patient experience that results in the elevated levels of emotional well-being and confidence in their treatment regimen.(12)

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Conflicts of interest

The authors have no conflicts of interest to declare

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