Pharmaco-economic evaluation of Therapeutic Drug Monitoring of 5-Fluorouracil in the treatment of Colorectal Cancer

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Bouchenak F [1], Laoufi NR [1], Mehdi L [1], Membrouk S [1], Abdalli I [1], Sobhi K [1], Oukkal M [2], Bouzid K [2]

[1] Faculty of Pharmacy-University of Algiers. [2] Faculty of Medicine-University of Algiers. ALGERIA

ABSTRACT

OBJECTIVES: Colorectal cancer (CRC) is one of the most frequently diagnosed cancers worldwide. 5-Fluorouracil (5-FU) is a chemotherapy drug commonly used for treating CRC. However, dosing based on body surface area (BSA) can lead to a large variability in blood concentrations and adverse effects (AEs). Therapeutic drug monitoring (TDM) of 5-FU has shown promising outcomes in optimal dosing, improved efficacy, and reduced toxicities. This study evaluates the budget impact of implementing TDM of 5-FU in CRC patients. **METHODS:** A budget impact analysis (BIA) was conducted from the payer's perspective over a five- year time horizon. The study population included stage 3 and 4 CRC patients at Beau-Fraisier Cancer Treatment Center in Algiers, Algeria. Treatment costs, AE management costs, and TDM costs were evaluated. Two scenarios were analyzed: current practice without TDM and a future scenario with a 20% annual increase in TDM adoption. **RESULTS:** Implementing TDM leads to significant cost savings compared to current practice. In the future scenario, the total budget over 5 years is USD 740,294.38 compared to USD 956,787.89 with current practice, with a total savings of USD 165,493.51. The incremental budget increased each year, from € USD 10,631.0 in 2025 to USD 56,173.0 in 2029. Per patient, TDM saves an average of USD 195.38 annually and USD 976.90 over 5 years. The cost savings resulted from a reduction in AEs with TDM implementation. **CONCLUSIONS:** Adopting TDM of 5-FU in CRC patients has shown a promising solution to reduce the economic burden of the current treatment practice. The budget impact is substantial at a single center and suggests a more prominent impact if implemented nationwide. These findings support the cost-effectiveness of implementing TDM in clinical practice for CRC treatment with 5-FU.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths worldwide **[1]**. 5-Fluorouracil (5-FU) is the most common chemotherapy agent to treat CRC **[2]**. The clearance of 5-FU varies among individuals, leading to variability in the doses reaching cancer cells. Consequently, some patients may receive insufficient doses for optimal effectiveness, while others may experience toxicity due to high circulating doses **[2]**. Research and clinical trials have indicated that therapeutic drug monitoring (TDM) is a valuable tool for enhancing effectiveness and reducing adverse effects of 5-FU. TDM involves measuring the plasma concentration of 5-FU and calculating the Area Under the Curve (AUC) over time witch is considered as the most relevant pharmacokinetic parameter concerning the effectiveness and toxicity of 5-FU **[3].**

OBJECTIVE

This study evaluates the budget impact of implementing TDM of 5-FU in Algerian CRC patients.

METHOD

This study compared two medical interventions in a retrospective observational study by analyzing existing data from clinical databases and medical records.

A budget impact analysis (BIA) was conducted (Payer's perspective from 2025 to 2029) to evaluate the costs associated with two medical interventions for treating CRC: Body surface area (BSA)-based dosing and Pharmacokinetic (PK)-based dosing of 5-FU at center level.

The study population included stage 3 and 4 CRC patients at Beau-Fraisier cancer Treatment center in Algiers. Data were primarily extracted from patients treated in 2022. Using the natural growth rate in Algeria from 2025 to 2029, we obtained statistics concerning the number of patients included in the analysis. The patients eligible for our study include patients with stage 3 and 4 CRC.

were evaluated :

- Treatment costs;
- AE management costs (grade 3 and 4 toxicities, CTCAE guidelines **[4]** and its management according to the European Society of Medical Oncology (ESMO) guidelines **[5]** and American Society of Clinical Oncology (ASCO) **[6]**);
- TDM costs (using UHPLC-DAD method developed and validated according to the ICH M10 at the Toxicology laboratory of central Army Hospital).

Two scenarios were analyzed :

- **Scenario 1**: current practice without TDM (BSA-based dosing)
- **Scenario 2**: with a 20% annual increase in TDM adoption (PK-based dosing) from 2025

Table 1. AEs and their respective frequencies before and after TDM. **[7]**

Adverse Effect	Frequency of AEs before TDM	Frequency of AEs after TDM
Diarrhea	12.10%	4.00%
Nausea and vomiting	6.10%	3.40%
Anemia	6.50%	2.80%
Neutropenia	13.60%	3.50%
Thrombocytopenia	4.30%	0.10%

RESULTS AND DISCUSSION

a. Market share

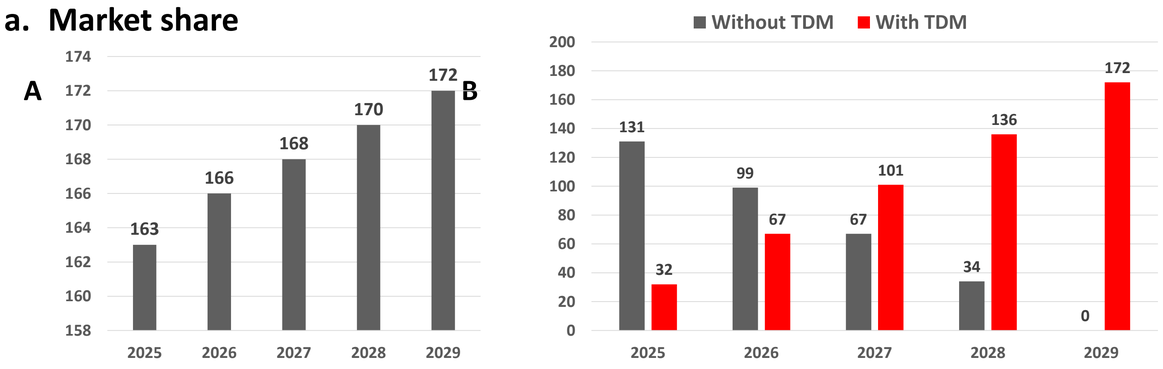

Figure 1. A: Eligible population scenario 1. **B**: Eligible patients for each scenario.

b. Costs associated with the treatment of CRC, AEs, and TDM

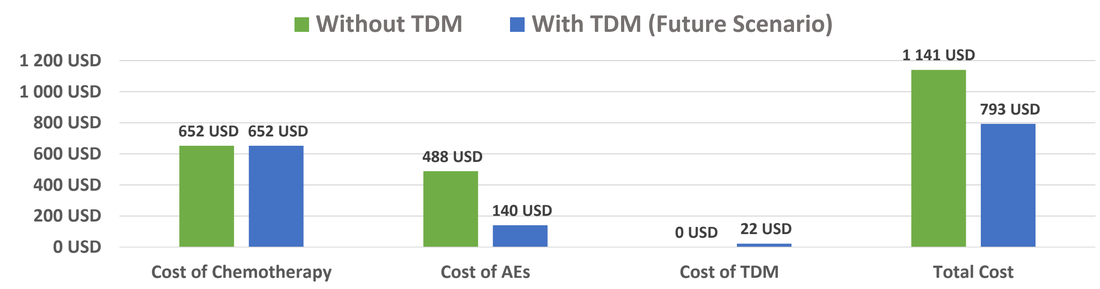

Figure 2. Cost of chemotherapy, AE management and TDM of 5-FU per patient.

The cost savings indicated in this BIA primarily arise from reducing AEs and the associated toxicity management costs when patients receive TDM. **Figure 2**

c. Incremental Budget over five years

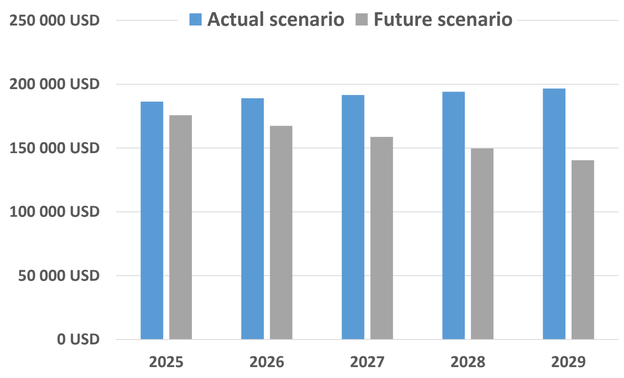

Figure 3. Budget Impact Model of each scenario over 5 years.

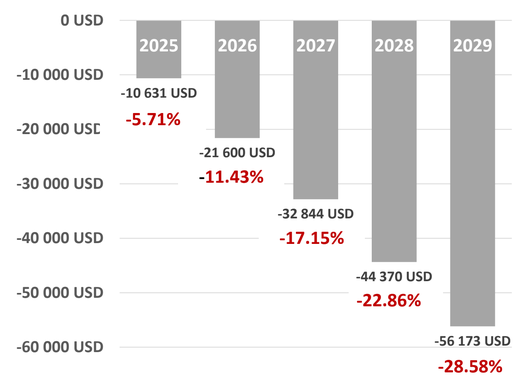

Figure 4. Incremental Budget Future Scenario.

The incremental budget (Future budget - Current budget) is shown in **Figure 4**. The incremental budget increases each year as more patients receive TDM.

Similar results were observed in a study by **Goldstein et al. [8]** in 2014. A cost-effectiveness analysis explored the potential benefits and costs associated with TDM of 5-FU in CRC patients. The model developed by Goldstein et al. incorporated data from clinical trials and published literature to estimate the risk of AEs, treatment efficacy, and costs associated with 5-FU toxicity. The analysis revealed that TDM resulted in a reduction of AE's and improved quality-adjusted life years. Although TDM incurred additional costs, the overall cost of implementation outweighed the costs associated with severe AE's observed with traditional BSA dosing methods. The study concluded that TDM in the FOLFOX regimen was cost-effective.

Erku et al. [9] conducted a similar study, developing a semi-Markov model to assess the cost-effectiveness of PK-dosing vs BSA-dosing of 5-FU in mCRC (metastatic colorectal cancer) patients, concluding that PK-dosing of 5-FU represents a cost-effective allocation of healthcare resources for treating mCRC in Australia.

This BIA was conducted in one treatment center only, the cost savings are substantial when TDM is implemented, suggesting the potential for an even more significant financial benefit if TDM was adopted on a national scale. The Beau-Fraiser treatment center represents approximately **2.72%** of CRC patients in Algeria. Extrapolating the cost savings observed in this study on a larger scale would magnify the economic impact significantly.

Even though the BIA has demonstrated promising outcomes in terms of an overall decrease in budget when adopting TDM, some limitations were encountered when conducting the analysis:

- Only included direct costs related to treatment without acknowledging indirect costs that could impact the results of the BIA;
- Cost of treatments and TDM were based on estimates and may not reflect real-world circumstances.

It's important to note that implementing TDM on a national scale would require investments in equipment, training, and personnel at cancer treatment centers throughout the country. Nonetheless, the potential long-term savings related to AE management and improved clinical outcomes suggested by other studies could counteract these initial costs.

CONCLUSION

The current treatment practice represents a significant economic burden, requiring necessary measures to prevent a continuous increase in costs. TDM represents a promising solution to reduce the economic burden by ensuring a more safe and accurate treatment practice while reducing the costs associated with treatment. Further studies could support current findings with more accurate data; however, this BIA serves as a strong starting point and provides a solid foundation for such efforts.

CONTACT

f.bouchenak@univ-alger.dz

REFERENCES