Budgetary Impact of Pre-Therapeutic DPD Deficiency Screening in Fluoropyrimidine-Treated Cancer Patients in Algeria

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ABSTRACT

OBJECTIVES: Fluoropyrimidines (FPs) are anti-cancer drugs widely used in oncology. Between 10-40% of patients undergoing FP treatment experience severe toxicity, which can lead to hospitalization and even death in 1% of cases. This toxicity is exacerbated by a deficiency in dihydropyrimidine dehydrogenase (DPD), a key enzyme which inactivates more than 80% of the 5-Fluorouracil administered and is responsible for the conversion of uracil (U, natural subtract) into dihydrouracil (UH_2). Pre-therapeutic screening for DPD deficiency, through U testing, is recommended by the European Medicines Agency and the French Health Authority. The UH_2/U ratio can also be used. The objective of this study is to determine the cost and budgetary impact of this screening in Algeria. **METHODS:** Cost estimates for implementing the screening were conducted using two testing techniques: U by UHPLC-DAD and the UH_2/U index by UHPLC-MS/MS. A budget impact analysis (BIA) was conducted from the payer perspective over a 5-year horizon, including cancer patients treated with FP in an Oncology service. Costs associated with managing adverse effects and screening were evaluated. Two scenarios were examined: current practice without screening and a future scenario with screening. **RESULTS:** Over a five-year period, 2,418 patients, representing 94.95% of the eligible population at the Cancer Center, receive fluoropyrimidine treatment. The implementation of screening in a single center costs USD 58,227.0 with UHPLC-DAD and USD 98,120.0 with UHPLC-MS/MS. Compared to the current scenario without screening, early screening by UHPLC-MS/MS and UHPLC-DAD could generate savings over 5 years estimated at USD 96,656.16 and UD 49,165.90 respectively. **CONCLUSIONS:** Screening for DPD deficiency, despite requiring initial investment, offers significant benefits by preventing severe complications and reducing costs associated with Fluoropyrimidine toxicity. Potential savings at a single center could support expanding screening on a larger scale, thereby improving the management of anticancer treatments in Algeria

INTRODUCTION

Fluoropyrimidines (FPs) such as 5-Fluorouracil (5-FU) are antimetabolites drugs **[1]** the most commonly prescribed for the treatment of various solid tumors (breast, digestive tract as well as neck and skull tumors) **[2-4].** FPs can cause toxicity in 10 to 40% of patients **[2,4]** and may lead to death in 0.1 to 1% of cases **[4,5**]. These toxicities are aggravated in case of dihydropyrimidine dehydrogenase (DPD) deficiency, the enzyme responsible for inactivating more than 80% of the dose of 5-FU administered **[3,6].** DPD also catalyzes the conversion of Uracil (U), its natural substrate, into Dihydrouracil (UH2). Since 2018, the French National Authority for Health and the French National Cancer Institute have recommended pre-therapeutic screening for DPD deficiency by determining the uracilemia level **[7]**, which will become systematic in France in January 2019. A practice also recommended at European level **[8]**. In Algeria, there are no recommendations concerning early screening for this deficiency.

OBJECTIVE

The aim of this study is to determine the cost and medico-economic impact of implementing pre-therapeutic screening for DPD deficiency in Algeria.

METHOD

A budget impact model (BIM) was developed to assess the financial implications of implementing a hospital-wide DPD deficiency screening unit. The data was consolidated in an Excel 2019 model, taking into account the following elements:

- Relevant epidemiological data (Beau Fraisier anticancer center…);
- The 5-year time horizon: from 2024 to 2028;
- The perspective: from the point of view of the Algerian payer.

The model also incorporates the market shares of the various comparators and evaluates the costs of managing adverse events (AEs) grade 3 and 4 (CTC-AE) for the **two scenarios** studied:

- **Scenario 1** (current scenario): without screening for DPD deficiency

  = **Cost of managing G3, 4 AEs**

  The management of AEs is based on guidelines issued by the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the experience of oncologists in the field.

- **Scenario 2** (future scenario): after implementation of the screening unit

  = **Cost of implementing DPD deficiency screening** + **Cost of AEs G3, 4** − **Cost of AEs G3, 4 Patients with DPD deficiency**

The Toxicology laboratory at the Dr Mohamed Seghir Nekkache hospital has two methods for screening for DPD deficiency, /UHPLC-DAD (not published) to determine the U and /UHPLC-MS/MS for U and UH2 (U and metabolic ratio UH2/U **[9]**). The Capitaine et al 2020. study was used to generate a scenario 2 in terms of toxicity in the event of DPD deficiency. **[10]**

The future scenario is based on the assumption that the introduction of screening for DPD deficiency will increase by 20% each year.

RESULTS AND DISCUSSION

a. Cost of implementing DPD deficiency screening unit

Table 1. Cost of implementation of screening by UHPLC-MS/MS

Item	Quatity	Cots in USD
Mass spectrometer with UHPLC	1	**74 839 USD**
C18 Column, 1.7 µm, 2.1 mm X 150 mm, 1/pk	10	5 334 USD
Pré-colonne C18 (1.8µm 5 x 2.1mm) 3/pk	20	17 277 USD
Validation reagents (ICH M10)	1	670 USD
Total		98 120 USD

Table 2. Cost of implementation of screening by UHPLC-DAD

Items	Quantity	Cots in USD
UPLC-DAD	1	**35 823 USD**
C18 Column, 1.7 µm, 2.1 mm X 150 mm, 1/pk	10	5 334 USD
Pre-colonne C18 (1.8µm 5 x 2.1mm) 3/pk	20	17 277 USD
Validation reagents (ICH M10)	1	13 USD
Total		**58 447 USD**

The cost of screening based on U according to a French reference is **USD 38 [12],** which is comparable to another Belgian reference (**USD 33** and **37** per patient) **[1].** In our study, the estimated cost per patient in euros is **USD 8.17** for U and **USD 12.60** for the metabolic ratio, showing a significant difference compared with the costs reported in France and Belgium.

b. Market share

Increase by 20% of screening for DPD deficiency each year (100% in 2028)

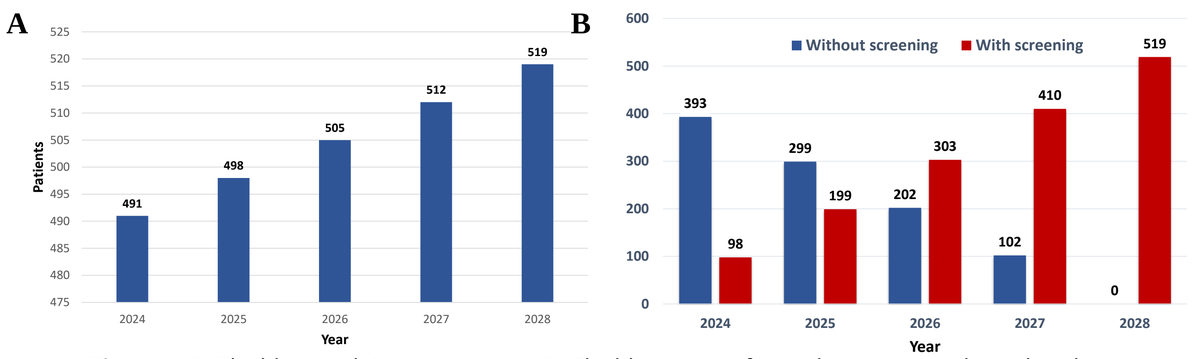

Figure 1. A: Eligible population scenario 1. **B**: Eligible patients for each scenario with market share

c. Incremental Budget over five years

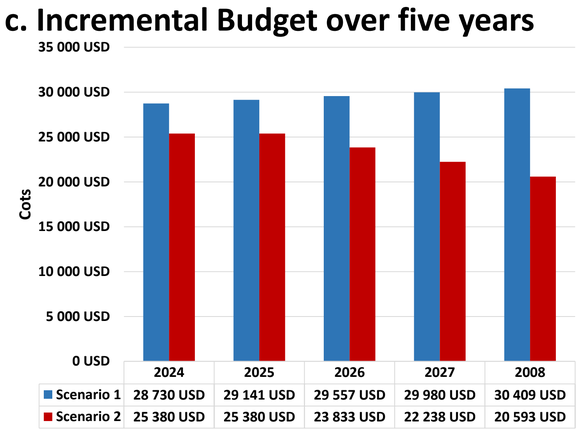

Figure 2. Costs evolution of each scenario using UHPLC-DAD.

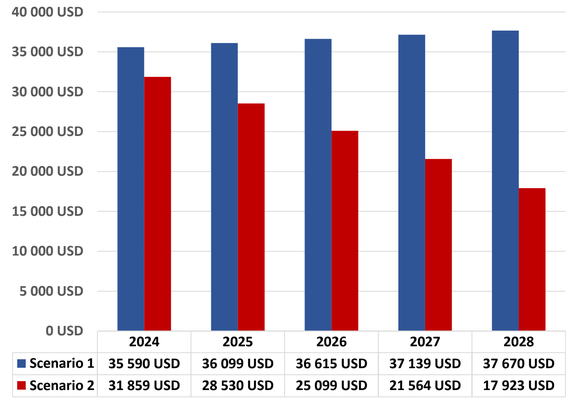

Figure 3. Costs evolution of each scenario using UHPLC-MS/MS

The incremental budget is shown in **Figure 4**. It has been calculated as the difference between scenario 1 and scenario 2, and represents the savings generated by the introduction of screening in the first year for both screening methods (UHPLC-DAD and UHPLC-MS/MS).

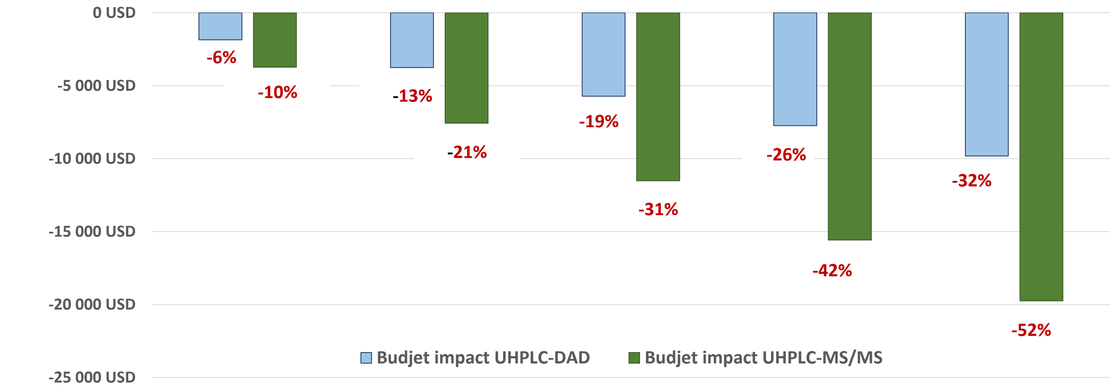

Figure 4. Incremental Budget Future Scenario by UHPLC-DAD or UHPLC-MS/MS.

Budgetary impact studies come to the same conclusion: introducing screening saves money on the management of toxicities. For example, in France, it has been shown that it would be possible to save nearly **USD 280** per patient by applying screening using the multiparametric method **[11].** Another study obtained similar results, with a budgetary impact of **USD 398** per patient **[12].** In our study, we noticed an average of **USD 32** per patient. It is important to note that these savings are calculated at the level of a single screening center, which partially explains why it's relatively low compared with the results of larger studies.

This analysis highlights the crucial importance of pre-therapeutic screening for DPD deficiency in order to reduce the costs associated with late management of toxicity requiring hospitalization. This would not only strengthen the national capacity to prevent the toxic risks associated with the administration of FP in cases of DPD deficiency, but would also help to improve the quality of oncology care in Algeria (precision medicine). It is also important to note that stage 5 or death were not included in this analysis because human life is invaluable.

CONCLUSION

While the implementation of a DPD deficiency screening unit represents a significant initial investment, it offers the possibility of avoiding the occurrence of serious toxicities, including outcomes that could lead to the death of the patient, while preventing a continued increase in costs linked to the adverse effects of treatment with fluoropyrimidines. Pre-therapeutic screening for DPD deficiency appears to be a promising solution for reducing these costs and enabling early intervention and appropriate management of patients on FP.

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REFERENCES