Market access and its impact on decision making in Spain. An example in acute myeloid leukemia.

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Introduction

- Different stakeholders are involved in the assessment of new drugs in Spain. There are specific entities at the regional, hospital level. At the national level, the Spanish Agency for Medicine and Health Products (SAMHP) performs the therapeutic positioning reports for new drugs.
- These evaluations include parameters as efficiency, safety, benefit/risk ratio, drug cost and its place in therapeutic line.
- Drug assessments are aimed to analyze and assess the added therapeutic value of new drugs according to scientific evidence and provide recommendations to professionals for the respective use of new drugs.
- In this analysis, a drug review was conducted to determine the current point of the management of acute myeloid leukemia (AML) and the benefit of new therapeutic interventions in elderly patients.

Materials and Methods

- A database has provided an overview of the evaluation of new medicines in Spain. This database summarizes the outcome measures in terms of efficacy, adverse events and economic parameters of these drugs in order to determine their therapeutic positioning given a clinical indication.
- This database also includes recommendations on the use of these drugs and evaluates the current treatment algorithms according to clinical guidelines and protocols.
- In the example of drug review performed for AML, one clinical guideline was reviewed in order to determine the pharmacological treatments available and the current treatment algorithms of disease.
- To draw conclusions on the use of drugs for AML, all drug assessments and therapeutic positioning reports published in Spain were identified. These correspond to 1 therapeutic positioning report from the SAMHP and 8 reviews at the regional and hospital level (Table 1).

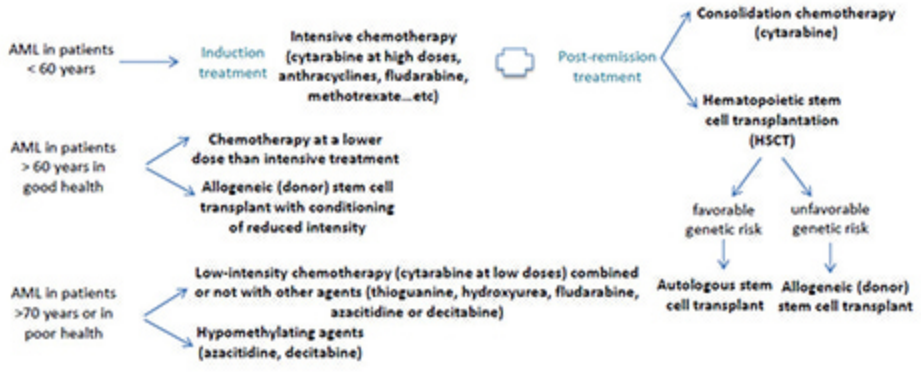
Table 1. List of drug assessment reports on AML

Name of the drug	Active substance	Pharmaceutical Laboratory	Authorization date	Drug assessment reports
DACOGEN® 50 mg powder for concentrate for solution for infusion	Decitabine	Janssen-Cilag International N.V	15/11/2012	• 2015 – Hospital Reina Sofía Córdoba • 2015 – Principado de Asturias Health Service (1) • 2015 – Principado de Asturias Health Service (2) • 2015 – H.U. Virgen de las Nieves • 2015 – CatSalut • 2015 – AETSA • 2014 – SAMHP • 2014 – CatSalut
VIDAZA® 25 mg/mL powder for suspension for injection	Azacitidine	Celgene Europe Ltd	09/01/2009	• 2015 –H.U. Virgen de las Nieves

Results

- Given the rapid progression of disease in AML, therapeutic intervention is urgent in these patients normally requiring hospitalization.
- The different therapeutic alternatives are assessed individually for each patient considering age, general state of health and prognostic factors (Figure 1).
- Conventional treatment can consist on intensive chemotherapy or a less aggressive treatment for those in poor health who cannot tolerate intensive treatment, which are best supportive therapy or cytarabine at low doses.
- Azacitidine and decitabine are new drugs that although provide a low response in remission of disease, their significant improvement in hematologic response and their reduced toxicity contribute to better results in survival and quality of life.

Figure 1. Pharmacological treatments for AML according to clinical guidelines



- The available evaluations of drugs used in AML correspond to the hypomethylating agents: azacitidine and decitabine (Table 2).
- The key primary endpoint that evaluates the efficacy of both azacitidine and decitabine is the median overall survival (OS).
- Other secondary outcomes evaluated are:
  - Progression-free survival (PFS)
  - Annual survival-%pacients
  - Event-free survival (EFS)
  - Relapse-free survival (RFS)
  - Complete remission (CR) and CR with incomplete platelet recovery
  - Complete cytogenetic remission
  - Duration of response in patients with CR
  - Relapse after CR

- One clinical trial has evaluated decitabine vs supportive therapy/cytarabine in patients with AML >65 years non candidates for standard induction chemotherapy.
- One clinical trial has evaluated azacitidine in elder patients with newly diagnosed AML with >30% blasts.

Table 2. Review of drugs evaluated in AML

Drug evaluated	Therapeutic positioning
Decitabine	- Decitabine has demonstrated a significant but modest improvement in terms of OS only in a second analysis of efficacy in comparison with supportive therapy/cytarabine. - This drug has showed superiority in secondary variables in some patients, specially in the variable complete remission with incomplete platelet recovery that has indicated a positive effect of decitabine in terms of clinical response and improvement of survival. - The subgroups of patients with blasts>30% and with type AML-de novo are estimated to obtain a potential benefit from this treatment based on the variable OS. - Treatment with decitabine should be reserved for patients who fulfill: ➢ Adult patients >65 years not considered candidates for standard induction chemotherapy neither to be included in clinical trials ➢ Adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who have not received previous treatment with azacitidine and the type of AML must be: non hyperleukocytosis or with hyperleukocytosis uncontrollable with chemotherapy (>40.000 leukocytes/mm3); >30% of blasts; intermediate-high cytogenetic risk. - It is recommended to evaluate the level of hemoperipheral recovery after each cycle of treatment and even it can be considered the interruption of treatment when there is disease progression or when complete remission or complete remission with incomplete platelet/hematologic recovery is not observed after 4 cycles of treatment.
Azacitidine	- Azacitidine has demonstrated significant differences versus a combination of conventional therapies (best supportive therapy, cytarabine...) in a sensitivity analysis for the variable median OS. - An analysis per subgroups of patients for the previous variable indicated a significant superiority of azacitidine vs the combination of conventional therapies in the following cases: <75 years, women, white population, poor citogenetic risk and AML with myelodysplasia-related changes. - Non recommendations on its therapeutic positioning have been formulated.

- The evaluation of the hypomethylating agents, decitabine and azacitidine, has demonstrated the efficacy of these therapies in treatment of AML.
- Specifically, both drugs azacitidine and decitabine have demonstrated to extend survival, control disease progression and improve quality of life of elderly patients or in a poor health state.
- The evaluation of the hypomethylating agent decitabine has demonstrated the efficacy of this therapy in treatment of AML.
- Given the aggression of disease and the low expectative of life for these patients, the efficacy outcomes of decitabine can be considered clinically significant.
- Regarding safety issues, decitabine has a similar safety profile than azacitidine related with hematologic reactions.
- Regarding economic issues, the cost of decitabine is superior to azacitidine.
- Overall, the scientific evidence demonstrated in favor of the two hypomethylating agents (azacitidine and decitabine) has corroborated that, although the clinical response based on complete remission is low, these drugs potentially extend survival of patients and allow to control disease and improve quality of life.

Conclusions

- This database on drug reviews has demonstrated to be a robust tool to assess the efficacy and safety measures of new drugs, including recommendations on crucial aspects for future drug assessments that can optimize the market access of a new drug.

Recommendations for future drug assessments

- It would be recommended to develop more studies based on a direct comparison of decitabine with azacitidine, which is a comparator more appropiate considered as an option for chemotherapy of low intensity. It would allow a better positioning of the two available hypomethylating agents.
- In contrast with other studies that have evaluated the administration of decitabine during 10 days, it is estimated that this regime provides better response and survival versus the 5 days-administration according with its posology. It would be recommended to corroborate this evidence, since a better regime of administration could reduce the number of visits to hospital.
- Finally, it would be necessary to develop more studies to define the best therapy for patients with AML of intermediate genetic risk, which has not been defined (chemotherapy or HSCT).

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