Progesterone Receptor and PTEN mutation as predictive factors of response to hormone therapy in metastatic endometrial cancer.

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Introduction

Hormone therapy is an effective treatment of metastatic endometrial cancer, with low toxicity and low cost. The response rate is interesting, up to 56% of clinical benefit rate is some studies. (Pautier et al., 2016) However, there is still no predictive factor of response well identified. The progesterone receptor is the only factor found, and could be proposed (grade C recommendation) before the introduction of the hormone therapy (ESMO-ESGO-ESTRO Consensus 2015).

The objective of the study was to found new predictive factors of response to hormone therapy in metastatic endometrial cancer by conducting an unsupervised analysis.

Characteristics	n (range) o % (n)
Age (years)	67 (61.5-74)
Weight (kg)	64.5 (56-75.25)
High Blood Pressure	55% (18)
Diabetis	18% (6)
FIGO Stage	
	1A 21% (8)
	1B 21% (8)
	2 5% (2)
	3A 18% (7)
	3B 3% (1)
	3C 21% (8)
	4A 3% (1)
	4B 10% (4)
FIGO grade	
	1 28% (11)
	2 44% (17)
	3 28% (11)
Histology	
HGSEC	16% (6)
EEC	82% (32)
Not Known	2% (1)
Initial ESMO group risk	
Low	15% (6)
Intermediate	10% (4)
High-Intermediate	10% (4)
High	54% (21)
Advanced	3% (1)
Metastatic	8% (3)
pN	
	0 72% (28)
	1 23% (9)
X	5% (2)
Radiotherapy	56% (22)
Brachytherapy	41% (16)
Hormone Therapy (HT)	
Progestins	72% (28)
Aromatase inhibitor (AI)	18% (7)
Sequential prgestatins and AI	5% (2)
Tamoxifen	5% (2)
Number of lines before HT	
	0 54% (21)
	1 31% (12)
	2 10% (4)
	3 3% (1)
	4 3% (1)
First line chemotherapy	
Carboplatine - Paclitaxel	69% (18)
Carboplatine	12% (3)
Carboplatine + Autre	4% (1)
Cyclophosphamide-Doxorubicine-Cisplatine	4% (1)
Others	12% (3)

Table. Patients characteristics. HGSEC: High Grade Serous Endometrial Carcinoma. EEC: Endometrioid Endometrial Carcinoma.

Figure: Results for immunohistochemistry (IHC), Next-Generation Sequencing (NGS, 20 most altered genes) and CGHarray (Comparative Genome Hybridation, 12 most altered genes). IHC: Red: expression – Pink: no expression. NGS: Black: mutation: Grey: Not Known, pale Grey: no mutation. CGHarray: Red: amplification, Green: Deletion, pale Grey: no alteration.

Material and Methods

We conducted a retrospective review of all cases of endometrial cases in two French cancer centers between January 2000 and January 2016.

Inclusion criteria were: metastatic endometrial cancer, treated by hormone therapy, histologic type endometrioid or serous, and FFPE sample (formalin-fixed paraffin-embedded) available. Exclusion criteria were hormone therapy received for an associated breast cancer and response not evaluable.

The main endpoint (EP1) was clinical benefit defined as partial or complete response of stability longer than 6 months. Secondary endpoints were response longer than 18 months (EP2) and overall survival (OS).

We performed a second histologic assessment by local experts, immunohistochemistry for estrogen (ER) and progesterone receptors (PR) and microsatellite instability-MSI- (hMLH1, hMSH2, hMSH6, PMS2).

We extracted DNA from FFPE tissue to perform molecular testing. We realized analysis by Next-Generation Sequencing (NGS) with a commercial panel testing 495 genes and CGH analysis (Comparative Genome Hybridation).

This study was approved by local ethic committee.

Results

On 1052 screened endometrial cancer cases, 46 completed inclusion criteria and 38 were included. DNA extraction was not possible for 3 cases, DNA quantity was not sufficient for 3 cases and NGS was not interpretable for 2 cases. Population characteristics were: 33 cases of endometrioid carcinoma, 6 tumors MSI, 30 tumors with at least one positive hormonal receptor.

3 women presented a thromboembolic event, whose one severe event inducing interruption of treatment.

In multivariate analysis, the only factor associated with EP1 was PTEN mutation (OR=5.92, p=0.047).

Percentage of progesterone receptor expression was associated with EP2. No MSI tumors presented a long time response.

Prognostic factors of OS were: age (OR=1.06, p=0.045) and at least one positive hormonal receptor (OR=0.26, p=0.031). PTEN did not reach significance (OR=0.32, p=0.077).

For EP1, the association PR+ - PTEN mutated was characterized by: sensibility of 0.47, specificity of 0.94, positive predictive value (PPV) of 0.89 and negative predictive value of 0.62.

For EP2, the association PR+ - PTEN mutated – MSI was characterized by: sensibility of 0.67, specificity of 0.96, PPV of 0.8, NPV of 0.93.

Conclusion

Testing PR, PTEN and MSI status could be an effective option to select good candidates to hormone therapy in metastatic endometrial carcinoma.