

Efficacy and tolerance of a simplified combination of Streptozotocine and epi-adriamycine in metastatic foregut neuroendocrine tumor (NET)

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Introduction

When surgery is not possible immediately, chemotherapy is the standard treatment of metastatic foregut neuroendocrine tumor (NET). Especially if the aim of the treatment is a tumor reduction for local treatment, because the tumor response rate to chemotherapy may be high.

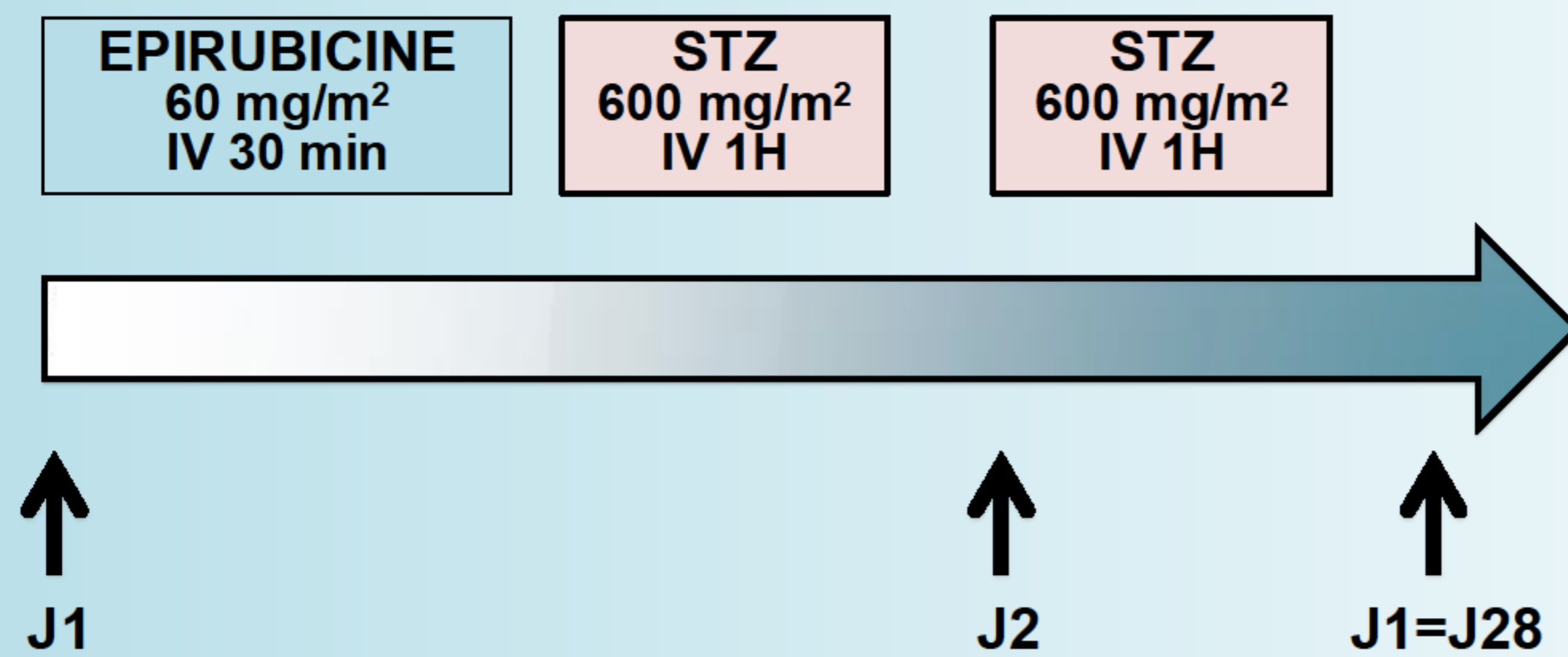
In this rare tumor, only few chemotherapy agents have been evaluated and since more than 30 years the combinations Adriamycine (A) and Streptozotocine (STZ) is one of the standard of chemotherapy regimens (Moertel et al, *N Engl J Med* 1992, 326 : 519-23) which may be proposed to patients with aggressive grade 2 metastatic pancreatic NET (PNET).

Yet, this combination has many drawbacks: as an heterogeneous response rate (from 25 % to 67%), an overall survival which depends on many factors and range from 11 to 19 months, and a poor tolerance when using the classical 5 days schedule of administration every 6 weeks with frequent nausea and vomiting. To overcome these limits since 2011 we have developed a simplified 2 days regimen repeated every 3 weeks.

Patients & Methods

- Retrospective analysis from the hospital database
- Eligibility criteria : patient with cytologically or histologically confirmed malignant neuroendocrine tumor, progressive and metastatic treated by simplified 2 days regimen Epi-Adriamycine & Streptozocine.

Chemotherapy protocol



The dose/intensity was equivalent to that used by Moertel & al.

Prevention of side effect

=> Prevention of nausea : Setron on D1+ D2, Aprepitant on D1 to D4, Corticoids (dexamethasone 12mg/d) on D1 to D5.

=> Prevention of nephrotoxicity : 2L of hydration / day (IV / oral)

- The tumor response was classified according to RECIST criteria, based on CT imaging or RMI imaging.
- Toxicities were graded according to WHO criteria at each cycle.

Results

Population

- 8 patients treated between January 2011 & December 2014

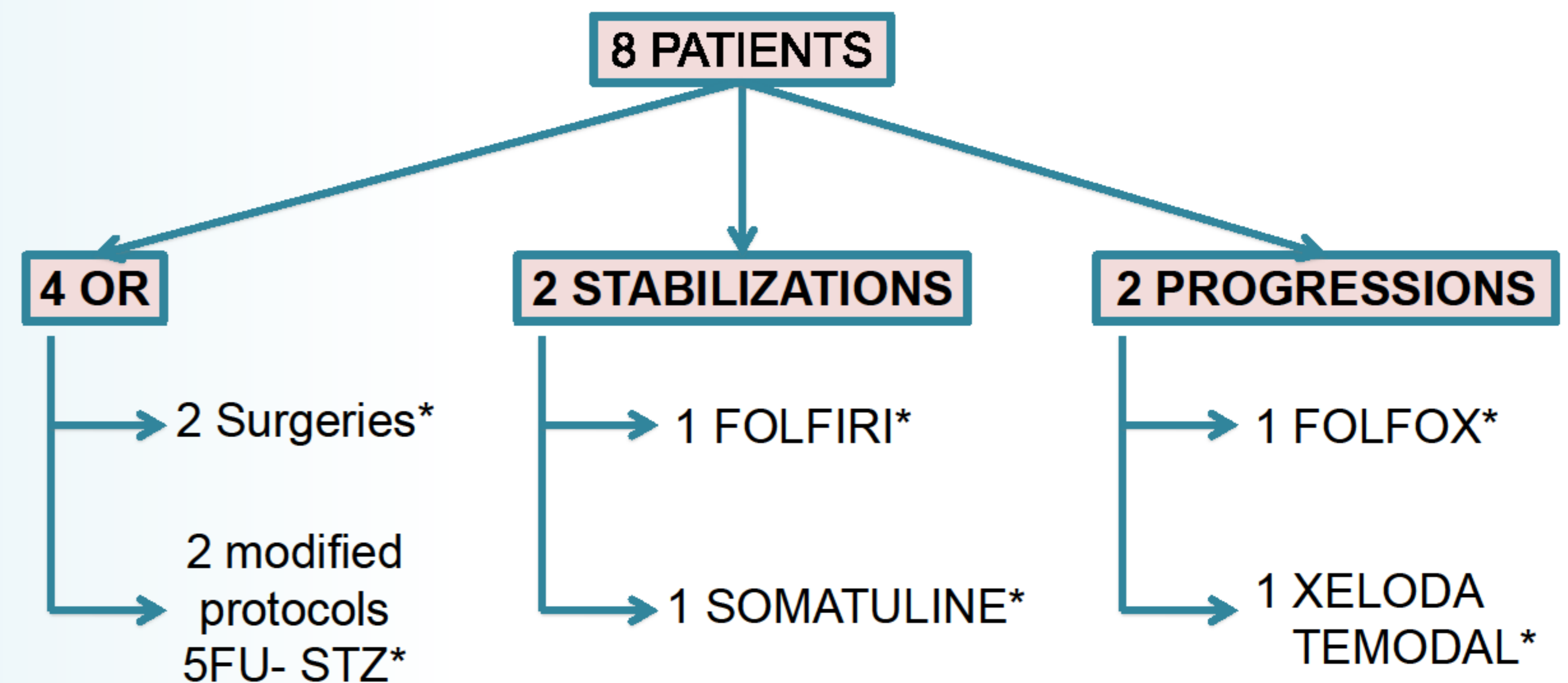
Patients	n = 8
Age (years)	
Median	66
Range	34-80
Female sex	2
WHO PS	
1	2
2	3
3	3
Primary tumor location	
Head of the pancreas	3
Tail of the pancreas	4
Gastric	1

Ki67 Grade	
1	0
2	7
3	1
Metastatic location	
Liver only	6
Liver + Bone + Lymph Node	1
Liver + Lymph Node	1
Prior Therapy	
None	6
Surgery	1
Embolisation	1

- All NET were well differentiated and 7/8 were without carcinoid symptom

Efficacy and secondary treatments*

- Median cycles of therapy administered : 3 (range : 1-7)



Tolerance

- No patient had acute nephrotoxicity or chronic renal insufficiency
- No dose reduction has been necessary
- 1 atrial fibrillation has been reported under Epi-Adriamycine

Side effect	Grade 0	Grade 1	Grade 2	Grade 3
Nausea /Vomiting	2/4	4/2	1/-	-/1
Diarrhea	5	-	1	-
Stomatitis	3	2	-	-
Asthenia	6	2	-	-
Leukopenia/ Febrile leukopenia	6/8	1/-	-	1/-

Conclusions

Our retrospective study on eight patients suggests that a simplified 2 days regimen of Epi-Adriamycine and Streptozotocine is feasible and active, its favorable profile compared to the traditional regimen on five days with moderate side effect and absence of renal toxicity, and its efficacy in the range of the traditional regimen are encouraging. This combination warrant to be evaluated prospectively in a controlled trial.

References

- Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med* 1992;326:519-23.
- Delaunoit T, Ducreux M, Boige V, Dromain C, Sabourin JC, Duvillard P, Schlumberger M, de Baere T, Rougier P, Ruffie P, Elias D, Lasser P, Baudin E. The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma; a judicious option? *Eur J Cancer* 2004 Mar40(4):515-20
- Dahan L, Bonnetain F, Rougier P, Raoul JL, Gamelin E, Etienne PL, et al; Fédération Francophone de Cancérologie Digestive (FFCD); Digestive Tumors Group of the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC). Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid tumors: FNCLCC-FFCD 9710. *Endocr Relat Cancer*. 2009 Dec;16(4):1351-61.

