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Inflammation markers and prognostic model of survival and toxicity in patients with advanced pancreatic cancer (APC) receiving palliative Gemcitabine-based chemotherapy: insights from the SAKK 44/00-CECOG/PAN.1.3.001

Piera Gargiulo

FINAL REPORT

Host Institute: SAKK (Swiss Group for Clinical Cancer Research), Bern, Switzerland
Mentor: Dr. Peter Brauchli

Home Institute – Head of department: Istituto Nazionale Tumori IRCCS, Fondazione G. Pascale, Naples, Italy - Dr. Sandro Pignata, head of the Medical Oncology Unit of the Uro-Gynecological Department

Introduction

Pancreatic cancer (PC) is one of the most lethal malignancies worldwide, and most patients are diagnosed too late for curative resection. Systemic gemcitabine-based chemotherapy has long been used as a standard therapy for patients with advanced pancreatic cancer (APC), however the prognosis differs greatly among patients. Therefore, it is clinically relevant to identify APC patients who are more likely to benefit from palliative chemotherapy with reduced risk of toxicity. Some clinical and laboratory parameters have been identified as being associate with prognosis in patients with APC. Recently some studies have showed the prognostic role of different inflammatory markers in many tumors, but few data exist for APC. In particular, derived neutrophil to lymphocyte ratio (dNLR) and neutrophil-platelet score (NPS), easily obtained from routine blood analysis, were found to be associated with cancer survival, but never explored in APC patients. Thus, it is necessary to evaluate and subsequently, integrate the available pretreatment factors in order to provide a prognostic model for predicting survival in patients receiving palliative chemotherapy. Furthermore, there is little evidence regarding toxicity predictors in APC patients.

Methods

The SAKK and the Central European Cooperative Oncology Group (CECOG) compared the efficacy and safety of gemcitabine (Gem) plus capecitabine (Cap) versus single-agent Gem in a randomized clinical trial (SAKK 44/00-CECOG/PAN.1.3.001). Briefly, this is a randomized, stratified, multicentre, phase III trial conducted at 30 centres in eight countries and comparing the efficacy and safety of gemcitabine (Gem) plus capecitabine (GemCap) versus single-agent Gem in advanced/metastatic pancreatic cancer. A total of 319 patients were enrolled between June 2001 and June 2004 and randomly assigned to receive GemCap or Gem and treatment was continued until disease progression or for a maximum of 24 weeks except in the case of unacceptable toxicity.

All patient characteristics available were assessed for prognostic significance, including inflammation markers. The derived neutrophil to lymphocyte ratio (dNLR) was calculated from peripheral blood counts as neutrophils divided by the difference of leukocytes and neutrophils. The neutrophils to platelets score (NPS) was calculated as follows: patients with a neutrophil count ≤7.5x109 /L and platelets ≤400x109/L scored 0, patients with neutrophils >7.5x109/L or platelets >400x109/L scored 1 and patients with both neutrophils >7.5 x109/L and platelets >400x109/L scored 2. All these parameters were tested in univariate analysis and then multivariable analysis to identify the independent predictors of mortality and toxicity (grade 3 or 4 adverse events). Then, based on regression coefficients, points were assigned to each risk factor to build up a prognostic score. The model performance was assessed with Harrel's C-statistic for discrimination

Results

Median survival of the study patients was 7.9 months (interquartile range 3.7–13.3 months). Independent predictors of mortality included increased Aspartate transaminase (ASAT), low performance status, increased derived neutrophil to lymphocyte ratio, increased Carbohydrate Antigen 19-9 (CA 19-9), low haemoglobin, presence of pain, presence of metastasis and increased alkaline phosphatase (ALP).
During the study, 117 patients experienced at least one grade 3 or 4 adverse event. Independent predictors of toxicity included white blood cells, ALP, renal function and bilirubin levels at baseline. Both models displayed moderate levels of discrimination (C-statistic 0.68 and 0.64 for mortality and toxicity, respectively) and adequate calibration.

Conclusion

To date the prognostic impact of inflammatory markers in pancreatic cancer is unknown and there is no prognostic score universally recommended to help clinicians in planning the therapeutic management of patients with advanced pancreatic cancer.
We explored predictors, including inflammatory markers, of survival and toxicity in a large cohort of APC patients treated with gemcitabine-based chemotherapy and analysing high-quality data from a multicentre randomized trial. We developed simple-to-use prognostic scores for both mortality and severe toxicity that can be useful in daily practice to identify patients with increased risk of death or toxicity and to plan the most appropriate therapeutic strategy in individual patients with the aim of improving both survival and quality of life.

List of presentations / publications resulting from the fellowship

Gargiulo P, Dietrich D, Herrmann R, Bodoky G, Ruhstaller T, Scheithauer W, Glimelius B, Berardi S, Pignata S, Brauchli P. Predicting mortality and adverse events in patients with advanced pancreatic cancer treated with palliative gemcitabine-based chemotherapy in a multicentre phase III randomized clinical trial: the APC-SAKK risk scores.
Ther Adv Med Oncol. 2019 Jan 2;11:1758835918818351. doi: 10.1177/1758835918818351.

Acknowledgements / personal statement

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References

- Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet 2016;388:73-85.
- Ter Veer E, van Rijssen LB, Besselink MG, et al. Consensus statement on mandatory measurements in pancreatic cancer trials (COMM-PACT) for systemic treatment of unresectable disease. Lancet Oncol 2018; 19:e151–e160.
- Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev 2017;58:1-13.
- van Soest RJ, Templeton AJ, Vera-Badillo FE, et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for men with metastatic castration-resistant prostate cancer receiving first-line chemotherapy: data from two randomized phase III trials. Ann Oncol 2015;26:743-9.
- Watt DG, Proctor MJ, Park JH, Horgan PG, McMillan DC. The Neutrophil-Platelet Score (NPS) Predicts Survival in Primary Operable Colorectal Cancer and a Variety of Common Cancers. PLoS One 2015;10:e0142159.
- Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for

Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007;25:2212-7.

- Bernhard J, Dietrich D, Scheithauer W, et al. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial--SAKK 44/00-CECOG/PAN.1.3.001. J Clin Oncol 2008;26:3695-701.

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