Systemic therapy in malignant mesothelioma: treat it or leave it

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PART III

Predictive & Prognostic Factors in Malignant Mesothelioma

Chapter 8

Prognostic value of CYFRA 21.1 in malignant mesothelioma: A brief report of the randomized phase II trial NVALT19

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CLINICAL TRIAL.

To the Editor:

Reliable prognostic and predictive markers can be an important support when choosing the optimal therapeutic path in an ominous disease like malignant mesothelioma. The cytokeratin 19 fragment (CYFRA 21-1) is one of the tumour markers for malignant mesothelioma with a prognostic impact. Earlier we noted that CYFRA 21-1 levels above the upper limit of normal (ULN, 1.9 µg per litre (µg/l)) were correlated with worse survival[1]. We aimed to confirm the prognostic value of CYFRA 21-1 in the series of NVALT19 patients. Recently, we reported a substantial progression free survival (PFS) benefit of switch maintenance gemcitabine therapy compared to best supportive care (median 6.2 months vs. 3.2 months respectively; hazard ratio [HR] 0.48; p = 0.0002) in this Dutch randomized NVALT19 trial in 130 mesothelioma patients. However, the doubling time of the PFS did not translate into a better overall survival for the patients in the active treatment arm [2].

As some studies in non-small cell lung and pancreatic cancer have pointed to a predictive effect of CYFRA 21-1 for response to chemotherapy [3,4,] we also analysed retrospectively whether CYFRA 21-1 might have any predictive value for the effect of gemcitabine in malignant mesothelioma.

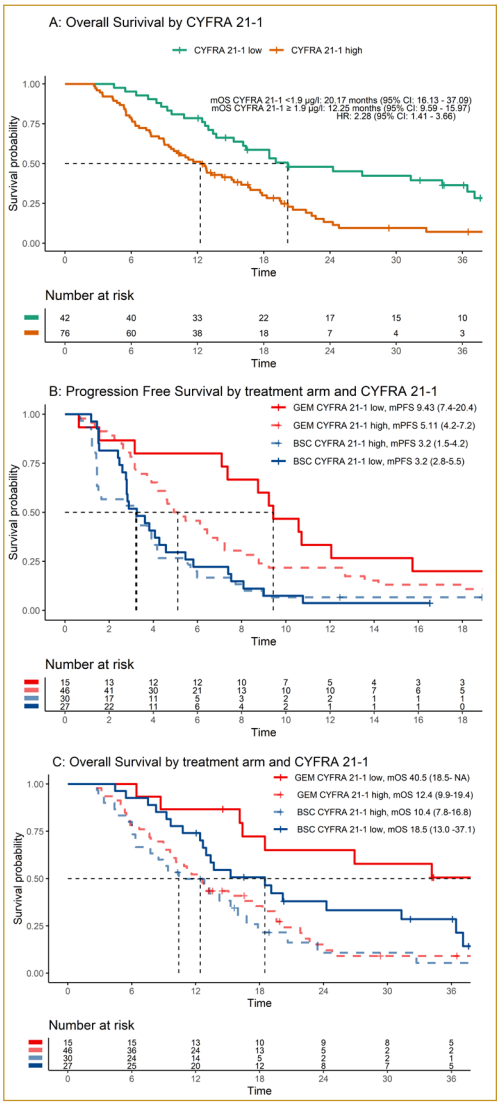

Fig. 1. Survival by Treatment and CYFRA 21-1 levels: Panel A: Overall survival by baseline CYFRA 21-1, stratified for pathological subtype and response to first line chemotherapy. Panel B: Progression free survival by treatment arm and CYFRA 21-1 level (serum levels below or above 1.9 µg/ l), stratified for pathological subtype and response to first line chemotherapy. Panel C: Overall survival by treatment arm and CYFRA 21-1 level (serum levels below or above 1.9 µg/l), stratified for pathological subtype and response to first line chemotherapy.

Prospectively collected baseline CYFRA 21-1 samples were available in 118 patients of the NVALT19 trial. We confirmed the prognostic value of CYFRA 21-1. Baseline serum levels below 1.9 µg/l predicted a better overall survival than higher levels (19.1 months vs. 12.3 months; HR for death 2.28 (95% CI: 1.11–3.66; see Fig. 1A). The progression free survival benefit of maintenance gemcitabine was seen both in patients with CYFRA 21.1 above and below 1.9 µg/l (see Fig. 1B). Patients with a CYFRA 21.1 baseline value <1.9 µg/l tended to have a survival benefit of maintenance gemcitabine in contrast to patients with baseline CYFRA value above 1.9 µg/l. Although subgroups were small, our current data suggested that only the subgroup with a low baseline CYFRA 21.1 might have a survival benefit of gemcitabine (see Fig. 1C).

The results of the current analysis of CYFRA 21.1 in malignant mesothelioma highlights its prognostic and potentially predictive value in this aggressive disease. Whether CYFRA 21.1 levels can be used to select mesothelioma patients for gemcitabine treatment needs conformation in an independent prospective study. Until then, reliable predictive biomarkers for response to systemic therapy like gemcitabine will be lacking and easily measurable prognostic markers will be the only prognosticator to assist in clinical decision making. In that respect, we are currently developing the MESOPRO score, that examines the prognostic value of CYFRA 21.1 combined with other prognostic factors in a large in divers cohort of malignant mesothelioma patients[5].

DECLARATION OF COMPETING INTEREST

CJG and VvdN have nothing to disclose. DvdB has participated in advisory boards of Roche, outside of the submitted work. PB has participated in advisory boards of Beigene, Aldura, AstraZeneca. PB has received consultancy fees for the hospital from Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb (BMS) outside of the submitted work. JAB reports sponsoring an investigator initiated- study by MSD and JAB has participated in advisory boards of Roche and Boehringer Ingelheim, funding to the NKI-AVL, outside of the submitted work.

1. W.A. Buikhuisen, J.A. Burgers, A.D. Vincent, C.M. Korse, R.J. van Klaveren, F.M.N. H. Schramel, N. Pavlakis, A.K. Nowak, F.LJ. Custers, J.H. Schouwink, S.JM. Gans, H. JM. Groen, W.FM. Strankinga, P. Baas, Thalidomide versus active supportive care for maintenance in patients with malignant mesothelioma after first-line chemotherapy (NVALT 5): an open-label, multicentre, randomised phase 3 study, Lancet Oncol. 14 (6) (2013) 543–551.

2. C.J. de Gooijer, V. van der Noort, J.A. Stigt, P. Baas, B. Biesma, R. Cornelissen, N. van Walree, R.C. van Heemst, M.-E. Soud, H.J.M. Groen, A.-V. den Brekel, W. A. Buikhuisen, G.P. Bootsma, F. Dammeijer, H. van Tinteren, F. Lalezari, J.G. Aerts, J.A. Burgers, Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial, Lancet Respir. Med. 9 (6) (2021) 585–592.

3. T. Zhao, Y. Jin, G. Mao, Y. Wei, G. Wu, X. Ye, Y. Zhou, G. Yuan, L. Gao, Y. Hong, Y. Chen, C. Hong, H. Zhou, D. Su, Z. Qin, L. Lu, CYFRA 21–1 is an early predictor of chemotherapeutic effectiveness in advanced nonsmall cell lung cancer: An observational study, Medicine 95 (52) (2016) e5748-e.

4. S. Boeck, C. Wittwer, V. Heinemann, M. Haas, C. Kern, P. Stieber, D. Nagel, S. Holdenrieder, Cytokeratin 19-fragments (CYFRA 21–1) as a novel serum biomarker for response and survival in patients with advanced pancreatic cancer, Br. J. Cancer 108 (8) (2013) 1684–1694.

5. C.J. de Gooijer, V. van der Noort, M. Disselhorst, J. Quispel-Janssen, L. Schunselaar, P. Baas, D. van den Broek, M. Stuiver, A. Scherpereel, D. Fennell, J. Creaney, A. Nowak, J.A. Burgers, MS07.07: Optimizing Survival Prediction in Malignant Mesothelioma; Development and External Validation of A Clinical Prediction Model (MESOPRO). 15th International Mesothelioma Interest Group Meeting 2021 (iMig 2021) 2021.