A New Prognostic Score Derived from Phase I Study Participants with Advanced Solid Tumours Is also Valid in Patients with Brain Metastasis

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Abstract. The purpose of this study was to evaluate the performance of a new prognostic score, originally developed in patients with advanced solid tumours participating in phase I trials, for patients with brain metastases treated outside of clinical trials. Seventy-one consecutive patients were assigned 1 point for more than two sites of metastasis, 1 point for albumin <35 g/l, and 1 point for lactate dehydrogenase >upper limit of normal. Forty-eight patients (68%) were assigned 0-1 points (favourable group) and 23 patients (32%) had 2-3 points (unfavourable group). Median overall survival from initiation of therapy was 5.5 months for those with score 0-1 versus 2.7 months for those with score 2-3, p<0.05. The new score appears to predict survival in other groups of patients with metastatic cancer, not only those participating in phase I clinical trials. Its performance should be evaluated in larger groups of patients and head to head comparisons of the established brain metastases scores with this new model should be made.

Prognostic indices represent useful tools in palliative cancer treatment; estimation of a patient’s prognosis in terms of overall survival might allow for tailored treatment, i.e. more aggressive approaches when these are likely to impact on survival, and focus on disease stabilization, symptom control and toxicity minimization when the disease is more advanced, or comorbidity limits the tolerability of aggressive therapy. In addition, prognostic indices are also used as inclusion/exclusion criteria for clinical trials and for comparison of results across different studies in relatively homogeneous patient groups. A number of different scores for patients with brain metastases have been published and validated, but, as discussed in a recent review (1), several questions remain unanswered. One of these is related to the fact that systematic assessment of the impact of blood chemistry values is lacking. Recently, Arkenau et al. published their validation of a prognostic score in 78 patients who were treated in 19 phase I trials at the Royal Marsden Hospital, Sutton, UK (2). This score includes albumin and lactate dehydrogenase (LDH), two parameters that were previously suggested as candidate factors influencing survival of patients with brain metastasis (3, 4). The purpose of the present analysis was to evaluate the prognostic value of this new score in patients with advanced solid tumours and brain metastasis treated outside of clinical trials.

Patients and Methods

Since 2007, a prospective database of patients with brain metastasis has been maintained at the Authors’ institution (5). This database was used to analyse the performance of the score published by Arkenau et al. (2, 6). Seventy-one consecutive patients were assigned 1 point each for more than two sites of metastasis, 1 point for albumin <35 g/l, and 1 point for LDH >upper limit of normal (ULN, defined as 205 U/l at the Authors’ institution). Overall survival was calculated by the Kaplan-Meier method. Fifteen patients were alive (without clinical event at the date of statistical analysis) and thus censored at the analysis date. Their follow-up was 2-20 months, median 9 months. All patients were treated with whole-brain radiotherapy and in 5 cases relapse was salvaged by radiosurgery. Comparison of actuarial survival curves was made by the log rank test. A p-value <0.05 was considered statistically significant.

Results

Sixty patients (84.5%) had primary lung or breast cancer, the others had gastrointestinal tumours, renal cell carcinoma, malignant melanoma and others. The median age was 63 years (range 34-85 years). Thirty-one patients (44%) received systemic chemotherapy, trastuzumab, erlotinib or sunitinib after brain irradiation. The percentage of patients
with systemic treatment was not significantly different between the favourable and unfavourable prognostic groups (44 vs. 43%). Regarding previous systemic treatment, 22 patients (31%) were treatment naïve, 27 (38%) had received one line, 15 (21%) had received two lines and 7 (10%) three or more lines. Thirty-four patients (48%) had elevated LDH and 7 (10%) decreased albumin <35 g/l at the time of treatment for brain metastasis. Ten patients (14%) had no extracranial metastases (6 with primary lung cancer, 3 with breast cancer and 1 with rectal cancer) and 28 (39%) had metastasis to two or more extracranial sites. The patients were assigned 1 point each if they had more than two sites of metastasis, e.g. brain plus lung plus adrenal gland, elevated LDH and albumin <35 g/l. Eventually, 48 patients (68%) were assigned 0-1 points (favourable group) and 23 patients (32%) had 2-3 points (unfavourable group). The median overall survival from initiation of radiotherapy was 5.5 months for those with score 0-1 vs. 2.7 months for those with score 2-3, \(p<0.05\) (Figure 1). A significant impact on survival was also found for each of the three individual factors (high vs. normal LDH, low vs. normal albumin and more vs. limited metastatic sites, \(p<0.05\); Kaplan-Meier curves not shown).

Discussion

In the original validation study by Arkenau et al. (2), patients with progressive cancer, mainly in the gastrointestinal tract and breast, were included. Their median age was 56 years and they had a median of two prior systemic therapies. In 37% of patients, more than two sites of metastasis were present. Patients with a score of 0-1 had a median overall survival of 7.6 months (33 weeks), those with a score of 2-3 survived for 3.6 months (16 weeks). As this score is based on easily available parameters and is straightforward, the question arises whether other groups of patients with advanced metastatic cancer can also be classified with this new tool. One possible example is patients with brain metastasis, which continues to represent a formidable challenge in oncology (7, 8). With increasing numbers of local and systemic treatment options, the issue of patient selection gains importance. A recent review has addressed the strengths and weaknesses of six different prognostic indices, published since the Radiation Therapy Oncology Group (RTOG) developed and validated the widely used 3-tiered prognostic index known as recursive partitioning analysis (RPA) classes (9), i.e. between 1997 and 2008 (1). The six indices are based on a different number of prognostic factors, i.e. (3-6). Surrogate markers of disease activity that are easy to measure and inexpensive, such as LDH and other laboratory parameters have repeatedly been shown to be independent prognostic factors for survival, although with different cut-offs and methods of analysis (3, 10-13). Some brain metastasis studies also confirmed that LDH, and lymphocyte counts might predict survival (3, 14). The recently reviewed prognostic indices for patients with brain metastasis unfortunately do not incorporate any of these parameters. The present analysis is the first evaluating a score based on surrogate markers of disease activity. It is interesting to note that survival can be predicted without any information on performance status and extent of intracranial disease, which are important parts of the established brain metastasis scores such as RPA. This finding suggests that further studies should examine whether the established scores, which are imperfect in predicting short-term survival (15), can be improved by adding surrogate markers of disease activity (in other words, is there any added value?). The patients analysed here were treated in Northern Norway with standard approaches outside of clinical trials. Their baseline characteristics are comparable to patients in other databases (reviewed by Nieder and Mehta (1)). A possible drawback of the study is the limited number of patients, but Arkenau et al. (2) included a comparable number. The score developed by these authors appears to predict survival in other groups of patients with metastatic cancer, not only those participating in phase I clinical trials. It appears that its performance in larger groups of patients should be evaluated and head to head comparisons of the established brain metastasis scores with this new model should be made aiming at individually tailored palliative treatment in patients with this serious condition, which continues to limit median survival to 3-6 months in unselected groups of patients.
References


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