© Adis International Limited. All rights reserved.

Bendamustine A Viewpoint by Patrick Schöffski and Arnold Ganser

Department of Haematology/Oncology, Hannover Medical School, Hannover, Germany

Bendamustine (Ribomustin®) is not a 'new' anticancer drug; its clinical use dates back to 1969, when the first objective responses (OR) were observed in patients with myeloma.^[1] In vitro data indicated only limited cross-resistance to common agents such as cyclophosphamide, cisplatin, melphalan and doxorubicin, and the compound induced more long-lasting double-strand breaks than other alkylators. In subsequent dose-finding studies in patients with solid tumours using the intermittent day 1 and 8^[2] and continuous 30-minute weekly intravenous infusion^[3] regimens, the drug was found to be very well tolerated. Mouth dryness, lymphopenia, fatigue and nausea were the most common adverse effects. In contrast to other commonly used agents, leucopenia and thrombocytopenia were not dose-limiting, and alopecia was not observed. Bendamustine, however, induced reversible lymphocytopenia, affecting all types of lymphocytes including B, T and natural killer cells. Mild cardiac toxicity was found in these and other studies^[4] in up to 16% of patients repeatedly exposed to the alkylating agent.

Bendamustine has shown promise as first- and second-line treatment of patients with breast cancer. Substituting bendamustine for cyclophosphamide in the CMF (cyclophosphamide/methotrexate/ fluorouracil) protocol extended the median duration of remission from 6 to 15 months in 61 chemotherapy-naive patients with metastatic disease. The bendamustine regimen (BMF) achieved a 52% OR, which compared well with CMF (46%). A randomised multicentre phase III trial comparing BMF with CMF as first-line treatment in 364 nonpretreated patients completed accrual in January 2001 and will help define the role of the drug in this setting. An ongoing randomised phase II trial is comparing weekly schedules of single-agent bendamustine and epirubicin in hormone-refractory patients with breast cancer.

A 3-drug combination of bendamustine with doxorubicin and vincristine was active in patients pretreated with CMF. 50% of 62 relapsed patients achieved an OR. Responses were seen in bone, soft tissue and visceral sites.^[5] As a single agent, bendamustine salvage treatment achieved a 27% OR in 36 pretreated patients with advanced breast cancer, and the efficacy was found to be independent of previous anthracycline treatment, consistent with the lack of cross-resistance seen in vitro. The role of bendamustine in patients previously exposed to either paclitaxel or docetaxel is being investigated in an ongoing phase II programme. Bendamustine is currently also being studied in combinations with mitoxantrone and trials have been designed to test bendamustine together with the monoclonal antibody trastuzumab in HER-2positive patients.

Based on the lack of cross-resistance and only partially overlapping toxicity patterns with commonly used agents for the treatment of breast cancer, further studies with bendamustine in this tumour type are clearly warranted. According to our phase I experience with the pharmacological profile of this alkylating agent, weekly combinations with taxanes or 2-drug regimens with oral fluoropyrimidines such as capecitabine should be considered for further testing.

References

- Anger G, Hesse P, Baufeld H. Behandlung des multiplen Myeloms mit einem neuen Zytostatikum. DMW 1969; 48: 2495-500
- Schöffski P, Hagedorn T, Grünwald V, et al. Repeated administration of bendamustine short infusions: a phase I study in patients with advanced progressive solid tumours. J Cancer Res Clin Oncol 2000; 126 (1): 41-7
- Schöffski P, Seeland G, Engel H, et al. Weekly administration of bendamustine: a phase I study in patients with advanced progressive solid tumours. Ann Oncol 2000; 11 (6): 729-34
- Reck M, Haering B, Koschel G, et al. Chemotherapie des fortgeschrittenen nichtkleinzelligen und kleinzelligen Bronchialkarzinoms mit Bendamustin – eine Phase II-Studie. Pnenumologie 1998; 52: 570-3
- Brockmann B, Geschke E, Schmidt UM, et al. Therapieergebnisse und toxische Nebenwirkungen der Kombination Cytostasan, Adriamycin und Vincristine als 'second-line' Therapie beim metastasierten Mammakarzinom. Geburtshilfe Frauenheilkd 1991; 51 (5): 383-6

