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Bendamustine is a hybrid antimetabolite and alkylating agent offering new therapeutic options for the treatment of non-Hodgkin lymphomas

Bendamustine is a rationally designed drug to combine both alkylating and antimetabolite functions with good tolerability. The cytotoxic effects of bendamustine differ from those of other alkylating agents, since in contrast to other alkylating agents, bendamustine activates a base excision DNA repair pathway rather than an alkyltransferase repair mechanism. Gene expression analyses showed that bendamustine has multiple mechanisms of action, including activation of DNA-damage stress responses and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe, a necrotic form of cell death that occurs during metaphase and is distinct from apoptosis (Leoni et al, Clin Cancer Res 2008).

In vitro results showed synergistic effects of bendamustine and rituximab (BR) (Rummel *et al.*, J Clin Oncol 2005). In view of these findings, recent studies are currently evaluating the potential efficacy of this combination). Alone or in combination with other chemotherapeutic agents, bendamustine has been shown to produce high clinical efficacy and acceptable tolerability in patients with various hematological malignancies, including Hodgkin's disease, indolent NHL, CLL and multiple myeloma.

In NHL, recent phase II studies with bendamustine monotherapy showed response rates between 67-75%, even in rituximab-refractory patients (Rummel *et al.*, J Clin Oncol 2005). When used in combination with rituximab or rituximab and mitoxantrone, response rates between 85-90% were shown (CR 36-60%) (Weide *et al.*, Leukemia & Lymphoma 2007). An interim analysis of a phase III study comparing CHOP-R versus BR as primary therapy suggests non-inferiority of BR with a favourable toxicity profile, especially regarding leukocytopenia, alopecia and infectious complications (Rummel *et al.*, ASH 2007).

In CLL, phase I/II trials with bendamustine mono- and combination therapy showed response rates of 56-95% in heavily pretreated patients. The first interim analysis of a phase III trial comparing bendamustine with chlorambucil in treatment-naïve patients, showed overall response rates of 68% and 39% and CR rates of 30% and 2%, respectively (Knauf *et al.*, ASH 2007). The median duration of remission was 18.9 months in the bendamustine arm as compared to 6.1 months after chlorambucil ($p<0.0001$) with a median progression-free

survival of 21.7 months and 9.3 months (p<0.0001), respectively.

The most common Grade 3-4 toxicities were in general hematological, mainly leukocytopenia, and to a lower extend thrombocytopenia and anemia; the incidence of non-hematological toxicities such as alopecia and gastrointestinal reactions were generally very low.

Perspectives: Bendamustine showed promising activity in phase II and III. Future study concepts are currently being performed looking at the potential of replacing complex multidrug combinations (FCR in CLL, R-CVP in NHL). Studies in histologic subgroups and especially medically non-fit patients will define the role of bendamustine in these patient populations with limited treatment options. Most importantly, based on its favorable side effect profile bendamustin represents one of the most favorable chemotherapy partners in combinations with novel molecularly targeted approaches.

References

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