The role of an all-oral chemotherapy containing lomustine (CCNU) in advanced, progressive Hodgkin lymphoma: a patient-friendly palliative option which can result in long-term disease control

In medicine, it is not infrequent that treatments in different institutions evolve over a period of time, by accepted use, with
modest background data. In the realm of palliative chemotherapy, it is clear that effective therapy can evolve this way. In this letter, we wish to draw attention to a very useful palliative regimen for the use in uncontrolled Hodgkin lymphoma (HL), which has been associated with long-term remission in some cases.

In the mid-1980s, the Scotland and Newcastle Lymphoma Group (SNLG) carried out a phase II study using lomustine, vindesine and bleomycin [1] involving 63 patients who required second-line treatment for HL. Thirty patients obtained complete response (CR), defined as total disappearance of all evidence of disease, and in 19 this was sustained. During the course of this study, we encountered a number of patients who, having failed primary and salvage approaches, wanted some active approach but wished to avoid the use of further injected cytotoxic drugs. As a result of the positive responses seen following use of the Lomustine-containing schedule, we developed an all-oral regimen comprising lomustine (CCNU), 100 mg/m² day 1; etoposide, 200 mg/m² days 1–3; chlorambucil 20 mg/m², days 1–4 plus prednisolone, 40 mg daily days 1–7, repeated at 6 weekly intervals until maximal response or until cytopenias prevented further use.

The schedule, designated PECC (prednisolone, etoposide, CCNU, chlorambucil) was assessed in 15 HL patients as a palliative therapy. Twelve (80%) patients had been extensively pretreated, 11 (73%) had extranodal disease and the majority had very poor performance status. The key advantage was the tolerability of the regimen from a subjective viewpoint. To our great surprise, CR occurred in eight patients (54%) and the overall response rate was 86% [2]. Of the patients with CR, three proceeded to autologous marrow transplant and have survived disease free.

The value of CCNU in HL was of course already well documented beginning in the early 1970s when it was assessed as a single agent [3, 4, 5] and found to be better than its sister drug carmustine when used alone [6]. In the 1980s, a number of investigators utilised CCNU in combination with other drugs for relapsed HL with moderate success [7–9]. Publications appeared at intervals in the 1990s with CCNU in different combinations [10–12]. In 1998, a report appeared detailing CCNU use in combination with vinblastine and mitoxantrone (MCV) [13] in 36 relapsed or refractory HL patients. A CR rate of 39% and partial response (PR, a reduction of 50% or more in size of all lesions present at diagnosis and no new lesions seen) rate of 50% were observed. The same authors updated their experience of the MCV schedule in 2006; rates of response and survival in advanced HL compared favourably with the results obtained after high-dose therapy with stem-cell transplant [14].

Following our own study in the 1980s, we did not continue with a further formal study but the PECC schedule was incorporated into the Northern Region UK Haematology Handbook (a menu of accepted treatments recommended for haematological conditions for a population of 3 million people) and was adopted by the SNLG centres in Scotland. While no specific outcome data were sought on the use of PECC, we did have in place the population-based data collection programme for lymphoma run by the SNLG for Scotland and Northern England [15], which ran from 1979 to 2002. This comprehensive dataset collected data on diagnosis and also recorded all treatments given in the patient’s lifetime along with the clinical outcome for each case. It is possible to interrogate the data collected prospectively to study PECC use in HL.

The register showed that PECC therapy was used in 92 patients from 1991 to 2002. Eighty patients (87%) were <60 years and 12 (13%) >60 years. Of these, one line of therapy had failed in 34 (37%) patients (the older the patient the more likely PECC was to be used as second-line therapy; all those >60 years received PECC as second-line therapy). Forty-five (49%) had failed two therapies and 12 (13%) more than two therapies. One patient had an unknown number of previous treatments. In those <60 years, 22 (27%) patients had CR, 15 (19%) PR, 20 (25%) static disease and 23 (29%) progressive disease. Overall response rate was 46%. In those >60 years, 7 of 12 patients (58%) obtained CR, the duration of CR was 3–47 months. Long-term disease-free survival was documented in 10 patients <60 years (12.5%). Of these 10 patients, four had high-dose therapy and blood stem-cell autologous transplant to consolidate remission, the remainder did not.

To assess toxicity, a retrospective review of the medical records of 25 of these patients was undertaken at one centre, it was noted that universally the doses were reduced from those described in the original paper as a result of leucopenia and/or thrombocytopenia usually after course 2. In particular, the lomustine dose was often capped at 120 mg per treatment and chlorambucil reduced to a dose of 30 mg per day. The required disease control was often achieved after three courses and this was the reason for discontinuation (8 patients); 7 patients discontinued due to cytopenia after three courses; in 10 patients, six courses were delivered with reduced doses after two treatments at full dose. Most infective episodes were dealt with on an outpatient basis and no fatality occurred in this group attributed to the chemotherapy. In this small review, it was noted that over time the steroid dose has been reduced to 5 days and increasingly dexamethasone as a single daily dose in the morning used instead of prednisolone in divided doses; the reasons given were less gastrointestinal side-effects, fewer tablets (dexamethasone 1 mg is equivalent to 8 mg prednisolone) for an equivalent dose, less insomnia and better appetite stimulation.

In conclusion, we propose that oral PECC is a valuable active palliative chemotherapy regimen which has very high patient acceptability, but we would now indicate that the original dose schedule should be modified to the following oral doses: lomustine (CCNU) 80 mg/m² day 1 (maximum 160 mg), etoposide 150 mg/m² days 1–3, chlorambucil 15 mg/sm² days 1–4 (maximum 30 mg/day), and to change the steroid to dexamethasone 6 mg/m² days 1–5. Close haematological monitoring is recommended.

Clearly, the response rate to PECC used as second-line therapy in relapsed elderly HL patients is good and we consider that a formal assessment of this protocol should be considered as second-line therapy in the elderly patient group (>65 years). Potentially, such a regimen has a place in the first-line...
management of frail elderly patients who would be unable to tolerate standard chemotherapy schedules [15].

acknowledgements

We acknowledge all the SNLG-affiliated centres for cooperation with the data collection programme. This data has not been presented at any meetings and does not exist in other written form.


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funding

Scotland and Newcastle Lymphoma Group (SCO 19772).

disclosure

None of the authors have any conflict of interest to disclose.

references


doi:10.1093/annonc/mdp527

Published online 9 November 2009