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Chemoimmunotherapy of chronic lymphocytic leukemia

Constantine S. Tam MBBS
Clinical Fellow

Michael J. Keating* MBBS
Professor of Medicine
Leukemia Department, Unit 428, The University of Texas MD Anderson Cancer, 1515 Holcombe Blvd, Center Houston, Texas 77025, USA

The past two decades have seen a major paradigm shift in the therapy of chronic lymphocytic leukemia (CLL), with the treatment goal shifting from symptom palliation to the attainment of maximal disease control using the most effective frontline regimens available, thus prolonging survival and possibly leading to cure. The most potent therapeutic regimens developed to date include the chemoimmunotherapy combinations incorporating purine analogs and monoclonal antibodies. We review the evolution of modern chemoimmunotherapy for CLL, and discuss current research directions for further refining the potency of these regimens.

Key words: purine analog; rituximab; alemtuzumab; monoclonal antibody; fludarabine.

THE EVOLUTION OF THERAPY FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Chemotherapy

CLL has traditionally been regarded as an incurable disease of the elderly, where the typical patient was expected to die 'with CLL' rather than 'of CLL'. Chemotherapy was with single-agent alkylators and was purely palliative in intent. The pursuit of maximal disease eradication was not regarded as a worthwhile goal in the majority of patients. This doctrine was reinforced by results of randomized trials showing no survival benefit in the early initiation of alkylator-based therapy for early-stage CLL.[1]

* Corresponding author. Tel.: +1 713 745 2376; Fax: +1 713 794 1602.
E-mail address: mkeating@mdanderson.org (M.J. Keating).

Recent evidence, however, contradicts this traditional view and shows that the majority of patients diagnosed with CLL will die of complications relating to CLL.[2] In addition, it is becoming increasingly apparent that the quality of remission achieved is an important determinant of outcome, with complete responders consistently enjoying superior survival than partial responders in studies with adequate follow-up.[3–7] Moreover, among patients achieving complete remission by conventional morphologic criteria[8], the eradication of 'minimal residual disease' (MRD), as evaluated by sensitive flow cytometric[9] or molecular[4] techniques, is associated with superior survival.[4,5,10] There has therefore been a major paradigm shift towards the exploration of maximally effective therapy in CLL, with achievement of the best possible response as the therapeutic goal.

Alkylating agents and purine analog monotherapy

Expectations of therapeutic outcomes using currently available chemotherapy strategies are outlined in Table 1. The CLL Trialists' Collaborative Group performed a comprehensive meta-analysis of studies comparing single-agent alkylator with combinations of alkylating agents, and found no significant survival advantage for patients receiving combination regimens.[1] Fludarabine was the first effective new agent to be extensively evaluated in CLL, achieving response rates of 50–60% in patients who failed traditional alkylating-agent therapy.[11] Fludarabine was soon studied in the frontline setting[3], where its activity was confirmed in three randomized comparisons, achieving superior major remission rates and prolonging remission duration when compared to alkylating agents as initial therapy.[12–14] More recently, early results from the LRF CLL-4 randomized comparison of chlorambucil versus fludarabine versus fludarabine-–cyclophosphamide in chemotherapy-naïve CLL confirmed superior complete response rate for fludarabine as compared with chlorambucil.[15]

Purine analog combination therapy

Based on in-vitro evidence of synergy between purine analogs and DNA-damaging agents[16], combinations of purine analogs and alkylating agents and/or anthracyclines were evaluated in clinical studies.[4,17–20] Of these, the most widely studied combination is fludarabine and cyclophosphamide (FC).[19,21–26] Preclinical studies show inhibition of cyclophosphamide-induced DNA damage when cells are exposed to fludarabine[16], and in turn exposure to cyclophosphamide enhances the incorporation of fludarabine metabolites into cellular DNA[27]; these observations suggest that constant exposure to both fludarabine and cyclophosphamide will be most effective. Indeed, the most common schedule of FC involves repeated daily doses of both fludarabine and cyclophosphamide.[19,21] Two randomized trials have compared this schedule of FC versus fludarabine alone as initial therapy of CLL, and both have found superior complete response rates and remission durations in favor of FC.[15,28] A second schedule of FC, pioneered by Flinn et al, comprises a larger dose of cyclophosphamide given on the first day only, in addition to 5 days of fludarabine.[25] This schedule has been evaluated against fludarabine as initial therapy in a randomized intergroup study, and was also found to have superior complete response rate and remission duration than fludarabine alone.[29]

Other combinations of fludarabine and DNA-damaging agents studied to date include fludarabine and mitoxantrone[20,30], fludarabine and chlorambucil[12,31], fludarabine and epirubicin[18], FC and mitoxantrone[4,32], fludarabine and mitoxantrone and cytarabine[33], and fludarabine and adriamycin.[17] None of these regimens has been formally