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CLL in the FCR era: managing toxicities and choosing optimal treatment post-relapse

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This publication is a summary of a recent presentation by Dr Constantine Tam, Consultant Haematologist at St Vincent's Hospital (Melbourne) and a Senior Fellow at the University of Melbourne. Dr Tam addressed haematologists in Auckland, Hamilton, Wellington, Christchurch and Dunedin, from 16–19 July 2012 on the treatment of chronic lymphocytic leukaemia (CLL). New clinical trial analyses point to exciting possibilities for CLL treatment paradigms.

The treatment of CLL

Treatment from the 1970s through the 1990s compared chlorambucil or single-agent chemotherapy with various combinations, and a number of trials compared early treatment versus treatment at the time of progression; the early treatment cohort did worse. The doctrine at this time was to observe until sufficient bulk requiring treatment, and then to administer the least toxic treatment, chlorambucil. From 2000 to 2007, chemoimmunotherapy approaches with fludarabine/cyclophosphomide/rituximab (FCR) and similar types of treatments improved progression-free survival (PFS) and probably also overall survival (OS), providing for the first time an advance over chlorambucil. In this era, patients were observed until disease bulk, then FCR was administered to every patient. Realisation that FCR does not suit all patients (i.e., older patients and those with high-risk cytogenetics) has led to biological risk stratification from 2008 through 2012, individualising therapy for best outcomes. On the basis of clinical data discussed later in this presentation, Dr Tam predicts a complete turnaround in the management of this disease in the next 5 to 10 years.

The FCR regimen

The German Chronic Lymphocytic Leukaemia Study Group (GCLLSG) CLL8 trial, a straightforward comparison between FC and FCR, revealed the superiority of FCR over FC without rituximab in patients with symptomatic CLL, prolonging PFS (rates at 3 years post-randomisation: 64.9% vs 44.7%, respectively) and OS (at 3 years post-randomisation: 87.2% vs 82.5%, respectively).[1,2] Importantly, this trial demonstrated that the initial choice of medication determines how long patients will live.

Based on the key trial, the current standard of care in CLL is a purine analogue and rituximab-containing regimen (e.g. FCR, or pentostatin combined with cyclophosphamide and rituximab [PCR]). Prolonged remissions lasting many years can be expected. These regimens may also improve OS.

However, some burning questions surround FCR.

- Firstly, how to manage elderly patients who do not tolerate this treatment?
- What supportive care measures are required?
- How to respond to relapse? What can be used to treat relapse, after initial therapy with the best treatment (FCR)?
- How to manage 17p- patients?

Optimal management of elderly patients

Elderly patients vary in levels of health, ranging from those who are exceptionally fit and obviously better than average, to those with chronic (multiple) diseases, comorbidity, disability and frailty. Older patients as a group do worse with chemoimmunotherapy. Analyses of data from the M.D. Anderson Cancer Center demonstrate that patients aged ≥70 have much lower rates of complete remission (CR) than those aged <70 years (46% vs 75%, respectively).[3] Thus, age is one of the major determinants in regard to how well patients respond to chemoimmunotherapy.

However, this is not to say that elderly patients do not benefit. In the Houston FCR experience, improvements in OS (as compared with previous generations of treatment) were observed in both younger and older patients. The problem is not efficacy, but rather, treatment administration is problematic because of poor tolerance; 82% of patients aged <65 years completed the scheduled 6 cycles of chemotherapy, compared with 51% of patients aged ≥65.

A number of potential solutions exist for successful treatment of older patients:

- Reduced intensity chemoimmunotherapy:
  - Pentostatin, cyclophosphamide, and rituximab (PCR)[4,5]
  - Sequential FCR[6]
  - Reduced-dose FCR and also FCR-Lite[7,8]
- "Non-chemotherapy" options.

In Germany, older patients are treated according to their scores on a Cumulative Illness Rating Scale:
Go-Go = the exceptionally fit; suitable for standard treatment (FCR)
Slow-Go = the not-so-fit (e.g. heart condition); suitable for reduced treatment (chlorambucil)
No-Go = suitable for supportive care only; palliate.

How Dr Tam manages older patients

Dr Tam uses dose-reduced FCR in older patients; there are very few older patients who cannot tolerate FCR for 1 day. FCR is quite easy to dose reduce – all patients can be treated with rituximab on Day 1, with the following adjustments as necessary to the subsequent 3-day FC schedule:

- Go-Go (<65–70 years) — FCR x 3 days
- Slow-Go (70–75 years) — FCR x 2 days
- No-Go (>75 or seriously unfit) — FCR x 1 day (this achieves a good outcome with minimal toxicity)

Many different prophylaxis schedules are used for supportive care, as shown in Table 1. Granulocyte colony-stimulating factor (GCSF) was only prescribed as secondary prophylaxis in the German trial (for an episode of febrile neutropenia); only 1 in 5 patients required GCSF. Likewise, Dr Tam's team at St Vincent's/Peter MacCallum prescribes GCSF on an as-required basis (for febrile neutropenia or when the cycle intensity is unable to be sustained). Acyclovir was discretionary in the M.D. Anderson trial and was not required in GCLLSG CLL8; the zoster infection rate was 4% in both trials. Dr Tam considers 4% to be a low enough risk to avoid prescribing acyclovir. He advises patients to watch out for mouth blisters and lesions or shingles-type pain and treat that early. PCP prophylaxis was discretionary at M.D. Anderson; the PCP rate without prophylaxis was 2.6%. The GCLLSG did not disclose how many patients were administered prophylaxis; no PCP episodes occurred. The historical fludarabine studies reveal that those patients at major risk for PCP include those exposed to steroids and those who have previously had chemotherapy. Dr Tam and colleagues consider that PCP is not required for those receiving first-line treatment and who are not exposed to steroids. Antifungal prophylaxis is not required; the risk of serious fungal infection is <1%. Dr Tam and team give nothing for the standard-risk patient. GCSF is administered if required for first-line; all patients should receive Bactrim® (sulfamethoxazole and trimethoprim) second-line onwards.

Table 1. FCR – supportive care

	MD Anderson 99-135	GCLLSG CLL8	St Vincent's / Peter MacCallum
GCSF	Discretionary	2° (feb neut) *Given in 18%*	2° (feb neut)
Acyclovir	Discretionary *Zoster w/o prophylaxis 4%*	No *Viral infection in 4%*	No
PCP	Discretionary *PCP w/o prophylaxis 2.6%*	If prolonged leucopenia > 7d *No PCP encountered*	If steroids or beyond 1st line
Antifungal	No *Aspergillosis in <1%*	No *Fungal infection in <1%*	No

GCLLSG = German CLL Study Group; GCSF = granulocyte colony-stimulating factor; PCP = *Pneumocystis carinii* pneumonia.

Clinicians who choose against primary prophylaxis can determine which patients are at highest risk by using a predictive model for infections, as depicted in Table 2 (using data from the Peter MacCallum Cancer Centre).[9] In the presence of more than 3 of 6 factors on the infection risk score, the risk of severe infection is 1 in 3 and the risk of severe neutropenia per cycle is 41%. Compared with the European and US criteria, this infection risk score fits with their criteria for primary prophylaxis.

Of the 6 infection risk score criteria, 2 are not applicable to frontline FCR:

- ≥3 previous therapies
- previous exposure to fludarabine.

Thus, patients receiving prophylaxis are older, have poor performance status, and have stage 1 neutropenia.

Table 2. Which patients are at highest risk?

INFECTION SCORE	INFECTION (% per pt)	G3+ INFECT (% per pt)	NEUT <0.5 (% per cyl)
0 – 2 **(standard risk)**	20	9	8
3+ **(high risk)**	66 *(p=0.0002)*	31 *(p=0.027)*	41 *(p<0.0001)*

Infection risk score:
Age >60 years
≥ 3 previous therapies
Previous exposure to fludarabine
Time to treatment >3 years
Performance status (ECOG) ≥2
Baseline absolute neutrophil count <2.0 x 10^9/L

FCR – unpublished pearls:

1. Patients who respond will usually do so after the first or second cycles – lymphocytosis should have disappeared and the nodes should be much softer, or already vanished. If lymphocytosis is still present after the second cycle, with persistent bulk that is not improving, FCR will be ineffective. Administering more FCR will result in more infections.
2. Beware of purine analogue-related cumulative myelotoxicity. In cases of sluggish recovery, Dr Tam will usually give patients a 2- to 4-week break to allow for a better recovery before their next dose. This avoids the risk of marrow wipeout, whereby the bone marrow becomes aplastic for months, sometimes for as long as up to a year.
3. Patients who respond well do not become infected (in general). Patients who progress through the first 4 cycles and are responding very well can be safely given the last 2 cycles, as long as their recovery is followed closely; in such cases, infections are rare during the last 2 cycles.

Management of FCR relapse

Two series of data exist; the larger is from the German CLL8 study, but with only a short follow-up. The scant available data demonstrate that FCR relapse occurring within 24 months is treated most commonly by rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); relapses >24 months are treated mostly by FCR or bendamustine/rituximab (BR).[10,11] Interestingly, the experience of the GCLLSG is that patients who relapse within 24 months will not do well, whereas those who relapse beyond 24 months have better survival. Second-line regimens consist of BR or R-CHOP, with mediocre outcomes; each are associated with 18 and 11 months PFS, respectively.

A median 120-month (10-year) follow-up of data from M.D. Anderson 99-135 (CLL treated with FCR-300 in the late 1990s) has given good insight into treatment of FCR relapse (data on file). At a median 55 months' follow-up after FCR failure 136 patients had relapsed and 12 were treatment-refractory; 129 received salvage treatment. Dr Tam stressed that patients who relapsed were not uniformly treated according to study protocol, but according to their treating physicians' decisions. The first insight is that, as with the German data, the major determinant of how long patients lived is how well they responded the first time: median OS was significantly shorter in patients with a first remission in <3 years compared with OS in those with a first remission ≥3 years. The sheer duration of how long patients stay in remission is a stronger predictor for subsequent survival than anything else, including mutations and cytogenetics.

The M.D. Anderson data also show that for those patients who relapse within 3 years, there is no effective salvage treatment. Median OS values range between 8 and 17 months for salvage regimens based on FCR, rituximab, alemtuzumab, NHL chemotherapy, and other therapies. The one exception is allogeneic transplantation. One in 4 patients relapsing within 3 years received a transplant; the only long-term survivors are the allograft recipients (median OS 12 months in the non-allograft cohort vs 93 months in allograft recipients). The major message is that if a patient relapses within 3 years of FCR, transplantation should be performed as soon as possible.

Patients who relapse beyond 3 years do quite well. FCR re-challenge is effective in this cohort, with superior OS to rituximab- and alemtuzumab-based salvage therapy, NHL chemotherapy, and other therapies. Lenalidomide was the only therapy to do as well as FCR. For patients who relapse after 3 years, probably the best standard treatment is to re-treat with FCR. Allografting is "unnecessary" in patients with a first response lasting >3 years; the M.D. Anderson data for the transplanted versus non-transplanted cohorts demonstrate no major advantage with allografting in patients relapsing beyond 3 years (unlike the <3-year relapse category, where transplantation is essential for survival). In Dr Tam's opinion, these data indicate that it is not urgent to transplant these patients – the data do not mean that transplantation does not work.

Acquisition of 17p- within 3 years is disastrous, whereas OS in patients acquiring 17p- beyond 3 years match those with Campath® (alemtuzumab) and steroid therapy of ~3 years.

FCR relapse: current state of affairs (M.D. Anderson 10-year data)

- Re-treat with FCR if first response >3 years
- Allograft ASAP if first response <3 years
- If 17p- beyond 3 years, probably avoid FCR again, but not a reason to panic.

P53 dysfunction – the "problem child" of CLL

17p Deletion, which causes loss of *p53* gene, is by far the worst subgroup. These patients tend not to respond well to chemotherapy and have a very short survival. Three-year OS (FISH) data from the German CLL8 study in the FC and FCR cohorts demonstrate improved survival in every subgroup except for 17p-.[2] However, while there is no statistical difference, M.D. Anderson data show that approximately 1 in 4 patients with 17p- who are treated with FCR do quite well, with reasonably durable remission lasting 3 to 5 years, or longer. Similarly, the German study data show 3-year OS at around 30% in the FCR series; such outcomes have never been seen in patients receiving FC, where there are inevitably no long-term survivors.

How to identify *p53* dysfunction in CLL? There are two ways in which *p53* may be knocked out: 17p deletion and *TP53* mutation. In theory, knocking out one *p53* leaves one functioning allele. However, it is now known that most patients with loss of the del(17p) locus have the other *p53* mutated. *p53* Mutations are just as bad as 17p-. Data from the UK show that both loss of the del(17p) locus with accompanying *p53* mutation on the alternative allele is associated with the worst PFS values; survival values are intermediate in patients with either *p53* mutation or 17p-, versus patients with neither the mutation or deletion.[12] Dr Tam has access to *p53* mutation screening technology, whereas many other clinicians have to rely on FISH, which fails to identify patients with 17p dysfunction in CLL. He predicts that within the next few years, there will be a requirement to start screening patients for these mutations as well.

Objective data on 17p- CLL first-line therapy

Clinical data do not support 17p- CLL first-line therapy with chlorambucil,[13] FC,[2] or BR.[14] The data also fail to support frontline alemtuzumab; although the associated CR rate is 27%, the PFS is <1 year (10.7 months).[13] In contrast, with frontline FCR or similar regimens,[2,15,16] as well as regimens combining alemtuzumab plus high-dose methylprednisolone[17] or high-dose dexamethasone,[18] the CR rate is around 25% in most series (the one exception is the German CLL8 study – only 5%). Median PFS is around 18 months for FCR or similar regimens. In contrast, the CR rates for alemtuzumab-steroid combinations are extremely diverse: 20% for one study[17] and 65% for the other,[18] whereas median PFS is the same as that with FCR (~18 months).

Frontline combination alemtuzumab-steroid treatment is not an easy regimen to give. Whereas FCR does not require any anti-infective therapy, alemtuzumab-steroid treatment requires Bactrim, valacyclovir, itraconazole, weekly cytomegalovirus (CMV) monitoring by PCR, and daily GCSF. Despite such prophylaxis, Gr3+ infections have been recorded in approximately 29% to 35% of patients and CMV reactivation in another 50%. In addition, Gr3+ glucocorticoid toxicity requiring admission have been recorded in 23%.[17] Of most concern to Dr Tam, out of 8 allogeneic transplants, 6 patients died of treatment-related mortality (TRM).[17] Despite this high rate, the accompanying discussion paper described this regimen as very suitable to give in transplants.

Allogeneic transplantation is effective

In a recent trial involving patients with poor-risk CLL, reduced-intensity conditioning allogeneic stem cell transplantation (alloSCT) demonstrated durable disease control, with long-term minimal residual disease (MRD)-negative survival in up to one-half of the patients independent of the underlying genomic risk profile (the 17p- cohort did just as well as any other group).[19] Similar data have been obtained from several other clinical trials.[20-26]

In summary:

- Dr Tam considers that p53 abnormal CLL does badly with any form of chemotherapy
  - Alemtuzumab plus steroid treatment is not necessarily better or safer, based on the current evidence
- Allogeneic stem cell transplantation is the only effective established therapy.

New targets in CLL

There are a number of new therapeutic targets in CLL, other than DNA damage (the target of classical chemotherapy) (as shown in Figure 1).[27]

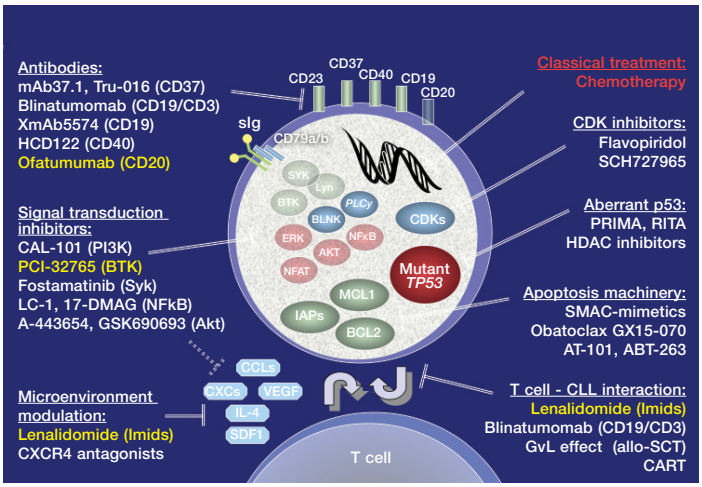

Figure 1. CLL: pathogenesis and treatment.[27]

Ofatumumab is available for compassionate use in Australia. This drug is approved in Australia for the treatment of relapsed/refractory CLL, based on its efficacy in patients with no conventional treatment options. These are patients who have failed fludarabine therapy and also alemtuzumab. Another group that is similar consists of patients who have failed fludarabine and who are considered unlikely to respond to alemtuzumab, e.g., patients with bulky lymph nodes. Historical data reveal an approximately 15% response rate in such patients with conventional therapy.[28] In this difficult patient subgroup, ofatumumab resulted in a 50% response rate lasting for about 6 months, in a clinical trial that subsequently led to FDA approval.[28]

Ofatumumab is undergoing testing in various combinations, such as FCO (ofatumumab and fludarabine/cyclophosphamide). Disappointingly, FCO appears to result in worse outcomes than FCR. Ofatumumab has shown limited activity in 17p- disease. However, Dr Tam is not convinced that ofatumumab is superior to rituximab at equivalent doses. Whereas rituximab is commonly given as 1g per dose, ofatumumab is given as 2g per dose for 8 doses, followed by 4 maintenance doses – a far greater antibody dose than rituximab. Data have demonstrated a clear dose-response rate in CLL, with 5g doses of rituximab achieving a 75% response rate.[29] However, such a dosing schedule is unaffordable and each 5g dose would take multiple days to administer.

Lenalidomide has multiple mechanisms of action. As single-agent therapy, lenalidomide has been associated with an approximately 30–50% response rate in patients with relapsed, chemorefractory CLL.[30-34] Instead of being immunosuppressive, lenalidomide may in fact assist in immune recovery, as evidenced by a reported case of refractory *Mycobacterial marinum* infection of the arm, which disappeared with lenalidomide treatment, with rapid increases in CD4 and CD8 blood counts.[35] A single-arm study has demonstrated reasonable response rates with first-line lenalidomide in elderly CLL cases.[36] Phase 3 studies are currently investigating lenalidomide single-arm versus chlorambucil single-arm in older patients. Data from M.D. Anderson suggest that OS with lenalidomide is at least as good as that of FCR in the elderly subgroup (data supplied by MJ Keating). Interestingly, lenalidomide has been associated with increases in serum immunoglobulins, indicating some rebuilding of the immune system.[36]

The ALLG CLL6 RESIDUUM trial is comparing lenalidomide consolidation with no consolidation in patients with CLL and residual disease following induction chemotherapy.[37] The investigators hypothesise that using lenalidomide in chemoresistant disease may help to convert MRD+ to MRD- and simultaneously renew the immune system.

B-cell receptor targeting: the way of the future?

Dr Tam suggested that the newer drugs that target B-cell receptors may completely change the way we manage CLL. These agents include dasatinib, fostamatinib disodium, and in particular, CAL-101 and the Bruton tyrosine kinase (Btk) inhibitor ibrutinib (PCI-32765).

Bruton's agammaglobulinaemia is an inherited immunodeficiency disease caused by mutations in the gene coding for Btk.[38] Patients with Bruton's agammaglobulinaemia are characterised by absent circulating B-cells, small tonsils and lymph nodes, and severe hypogammaglobulinaemia. The disease is also associated with frequent bacterial infections. Notably, immunoglobulin replacement therapy is associated with survival into mid-adulthood.

Ibrutinib is an irreversible oral blocker of Btk with a 30-fold higher specificity for Btk compared with other kinases. Its main side effect is diarrhoea. Ibrutinib is highly effective in relapsed/refractory CLL. In patients with refractory disease after 4 lines of treatment (the majority were fludarabine-refractory) who then received ibrutinib 420 mg/day or 840 mg/day, almost all patients responded and in an unusual manner: the rapid shrinking in nodal response was accompanied by an increase in absolute lymphocyte count and later, subsequent lymphocyte normalisation.[39] Dr Tam explains this phenomenon as a shifting of the CLL cells from the lymph nodes and spleen into the peripheral blood compartment, where they spontaneously die or become totally susceptible to chemotherapy.

There is a remarkable lack of resistance with ibrutinib in the studies to date, notwithstanding the currently short follow-up times. Responses are durable and ongoing.[39,40] To put these results into context, most CLL chemotherapies result in an approximate 3-month response in one-third of patients, after which time all patients ultimately relapse and die. In contrast, ibrutinib-treated patients are not relapsing. At this point in time, the CLL cell is unable to bypass Btk blockade.

Are we treating CLL the wrong way?

Elderly CLL is currently treated like acute myelogenous leukaemia (AML), with a large dose of chemotherapy in an attempt to eradicate as much disease as possible, followed by a period of watching and waiting for tumours to reappear. Should CLL instead be treated like chronic myelogenous leukaemia (CML), with indefinite suppression? Ibrutinib response curves are beginning to resemble those seen with imatinib for CML. While the patients will eventually require immunoglobulin replacements for hypogammaglobulinaemia, this consequence of Btk blockade is definitely preferable to CLL-related death.

Frontline ibrutinib has proven to be exceedingly well tolerated in 31 elderly treatment-naïve CLL patients, with an estimated 15-month PFS of 96% for both ibrutinib doses (420 mg/day and 840 mg/day) at a data cut-off of 13 March 2012 (data on file). Probably the most important feature of ibrutinib is that it is completely p53 independent. The experience at M.D. Anderson suggests that ibrutinib is the most effective therapy tested to date in 17p- CLL.

Is chemotherapy destined to die?

While it might seem logical to consider that ibrutinib will replace toxic CLL chemotherapy, updated M.D. Anderson trial data indicate otherwise. At a 10-year median follow-up, in patients treated with FCR, the PFS data show that a plateau may be emerging in approximately one-third of treated patients. Patients with mutated IgVH may have a particularly favourable prognosis. This observation raises the tantalising possibility that CLL may be curable with currently available chemotherapy, such as FCR. Mature follow-up from other studies, such as the CLL-8 study, will be required to confirm these observations from M.D. Anderson.

CLL: a new paradigm?

Dr Tam believes that CLL is a curable disease in young people. He predicts a new paradigm for CLL from 2013 onwards, as depicted by Figure 2.

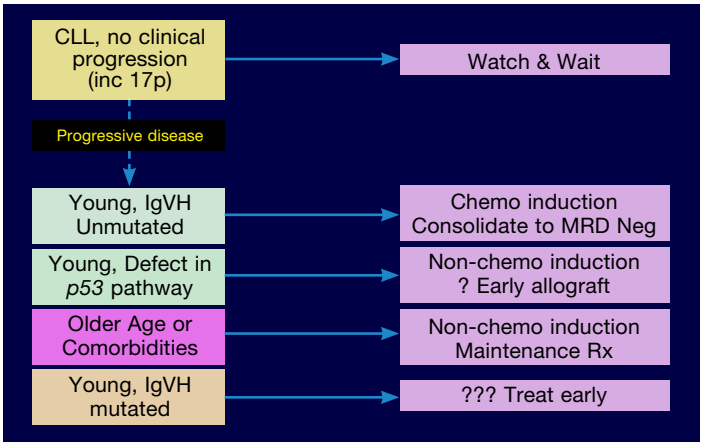

Figure 2. A new paradigm for CLL?

For CLL with no clinical progression (including 17p), a watch and wait strategy is feasible. Among those that develop progressive disease, patients who are young and IgVH unmutated should be treated the usual way. In patients who are young, have a defect in the *p53* pathway, and there is access to a drug like ibrutinib, the appropriate strategy is non-chemotherapy induction followed by early transplantation. For older patients, where treatment tolerance is an issue, the future may be to suppress the disease indefinitely with ibrutinib, or similar drugs. The most intriguing group will be younger patients with mutated IgVH, a fraction of whom may be curable with FCR chemotherapy. For these patients, it may be interesting to design clinical trials to address the question of whether earlier treatment may result in an increased proportion of patients remaining progression-free long-term.

Q&A session

Q: Do any data exist as to using the Btk class of drugs in a cyclical manner? Are there any preclinical data showing long-term B-cell-related side effects?

A: No. The animal models are very basic – determining only whether the drug works. With most drugs, using them in a cyclical manner encourages the development of treatment-resistant clones. The consequence of Btk blockade is well established, with the perfect in-human model. There is no doubt that immunoglobulin infusions will be required to prevent infections in patients undergoing prolonged Btk blockade. Although expensive for society, Dr Tam predicts that the overall cost compares favourably with the expenses of hospital admissions for infections and stem cell transplantation.

Q: The focus has been on Btk inhibition, but other drugs in the pipeline have shown promise.

A: Dr Tam is keen to initiate a service to offer comprehensive prognostic and tumour profiling for patients with 17p- CLL, in order to bank samples and gather the patient numbers to attract new drug trials in 17p- CLL to Australia and New Zealand.

Q: What is the optimal frontline induction for patients with 17p- CLL? Should we be using alemtuzumab and steroids, and what dose of steroids to use?

A: Dr Tam uses FCR, with a very low threshold for bailing out in those patients who do not respond well. As for steroid dosage, he believes that the German approach is more tolerable (two pulses of dexamethasone per month) than the UK approach of 10g methylprednisolone per week. He suggests that the dose of alemtuzumab as currently used may be too high; instead of 30mg 3 times weekly, there are abstracts from Italy suggesting that prolonged administration at lower doses may be better tolerated and similarly effective.

References

1. Hallek M, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). Presented at ASH 2008; abstract 325.
2. Hallek M, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164-74.
3. Tam CS, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008;112(4):975-80.
4. Lamanna N, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol. 2006;24(10):1575-81.
5. Kay NE, et al. Pentostatin and rituximab therapy for previously untreated B-CLL. Cancer. 2010;116(9):2180-7.
6. Lamanna N, et al. Sequential therapy with fludarabine, high-dose cyclophosphamide, and rituximab in previously untreated patients with chronic lymphocytic leukemia produces high-quality responses: molecular remissions predict for durable complete responses. J Clin Oncol. 2009;27(4):491-7.
7. Foon KA, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(4):498-503.
8. Mulligan SP, et al. The safety and tolerability of oral fludarabine, ±oral cyclophosphamide and IV rituximab therapy in previously untreated patients with chronic lymphocytic leukaemia (CLL) aged ≥65 years – interim analysis from the Australasian Leukaemia and Lymphoma Group (ALLG) and CLL Australian Research Consortium (CLLARC) CLL5 Study. Proceedings of the ASH Orlando 2010 Blood. Nov;116(21). Oral and Poster Abstr 699.
9. Tam CS, et al. A new model for predicting infectious complications during fludarabine-based combination chemotherapy among patients with indolent lymphoid malignancies. Cancer. 2004;101(9):2042-9.
10. Cramer P, et al. Second-line therapies after treatment with fludarabine, cyclophosphamide, and rituximab (FCR) or fludarabine and cyclophosphamid alone (FC) for chronic lymphocytic leukemia (CLL) within the CLL8-Protocol of the German CLL Study Group (GCLLSG). Abstr 2863. Presented at the 53rd ASH Annual Meeting and Exposition. December 10-13, 2011.
11. Jenke P, et al. Cyclophosphamide, adriamycin, vincristine and prednisone plus rituximab (CHOP-R) in fludarabine (F) refractory chronic lymphocytic leukemia (CLL) or CLL with autoimmune cytopenia (AIC) or Richter's transformation (RT): final analysis of a phase II study of the German CLL Study Group. Abstr 2860. Presented at the 53rd ASH Annual Meeting and Exposition. December 10-13, 2011.
12. Gonzalez D, et al. Mutational status of the *TP53* gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. J Clin Oncol. 2011;29(16):2223-9.
13. Hillmen P, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2007;25(35):5616-23.
14. Fischer K, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011;29(26):3559-66.
15. Bosch F, et al. Rituximab, fludarabine, cyclophosphamide, and mitoxantrone: a new, highly active chemoimmunotherapy regimen for chronic lymphocytic leukemia. J Clin Oncol. 2009;27(27):4578-84.
16. Tam CS, et al. De novo deletion 17p13.1 chronic lymphocytic leukemia shows significant clinical heterogeneity: the M. D. Anderson and Mayo Clinic experience. Blood. 2009;114(5):957-64.
17. Pettitt AR, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the national cancer research institute CLL206 trial. J Clin Oncol. 2012;30(14):1647-55.
18. Stilgenbauer S, et al. Subcutaneous alemtuzumab combined with oral dexamethasone, followed by alemtuzumab maintenance or allo-SCT in CLL with 17p- or refractory to fludarabine – interim analysis of the CLL20 trial of the *GCLLSG* and *FCGCLL/MW*. Abstr 920. Presented at the 52nd ASH Annual Meeting and Exposition, December 4-7, 2010.
19. Dreger P, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood. 2010;116(14):2438-47.
20. Schetelig J, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol. 2008;26(31):5094-100.
21. Sorror ML, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol. 2008;26(30):4912-20.
22. Khouri IF, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. Br J Haematol. 2007;137(4):355-63.
23. Brown JR, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. Biol Blood Marrow Transplant. 2006;12(10):1056-64.
24. Gribben JG, et al. Autologous and allogeneic stem cell transplantations for poor-risk chronic lymphocytic leukemia. Blood. 2005;106(13):4389-96.
25. Moreno C, et al. Allogeneic stem-cell transplantation may overcome the adverse prognosis of unmutated VH gene in patients with chronic lymphocytic leukemia. J Clin Oncol. 2005;23(15):3433-8.
26. Delgado J, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood. 2006;107(4):1724.
27. Zenz T, et al. From pathogenesis to treatment of chronic lymphocytic leukaemia. Nat Rev Cancer. 2010;10(1):37-50.
28. Wierda WG, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1749-55.
29. O'Brien SM, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol. 2001;19(8):2165-70.
30. Chanan-Khan AA, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006;24(34):5343-9.
31. Ferrajoli A, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood. 2008;111(11):5291-7.
32. Wendtner C. Final results of the phase I study of lenalidomide in patients with relapsed/refractory chronic lymphocytic leukemia (CLL-001 Study). Abstr 1376. Presented at the 52nd ASH Annual Meeting and Exposition, December 4-7, 2010.
33. Ferrajoli A, et al. The combination of lenalidomide and rituximab induces complete and partial responses in patients with relapsed and refractory chronic lymphocytic leukemia. Abstr 1395. Presented at the 52nd ASH Annual Meeting and Exposition, December 4-7, 2010.
34. Badoux X, et al. Combination of ofatumumab and lenalidomide in patients with relapsed chronic lymphocytic leukemia: initial results of a phase II trial. Abstr 2464. Presented at the 52nd ASH Annual Meeting and Exposition, December 4-7, 2010.
35. Awais A, et al. Rapid resolution of *Mycobacterium marinum* chronic skin infection during lenalidomide therapy for chronic lymphocytic leukemia. Clin Infect Dis. 2008;46(7):e69-71.
36. Badoux XC, et al. Lenalidomide as initial therapy of elderly patients with chronic lymphocytic leukemia. Blood. 2011;118(13):3489-98.
37. An Australasian, phase III, multicentre, randomised trial comparing lenalidomide consolidation vs no consolidation in patients with chronic lymphocytic leukaemia (CLL) and residual disease following induction chemotherapy. http://www.anzctr.org.au/trial_view.aspx?ID=335021
38. Chin TW. Pediatric Bruton agammaglobulinemia. Medline review. http://emedicine.medscape.com/article/885625-overview
39. O'Brien S, et al. The Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 induces durable responses in relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): follow-up of a phase Ib/II study. Abstr 983. Presented at the 53rd ASH Annual Meeting and Exposition, December 10-13, 2011.
40. Jaglowski SM, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases. J Clin Oncol. 2012;30:(suppl; abstr 6508).

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