Fludarabine Annex: cost-effectiveness

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1. Four different cost effectiveness analyses have been summarised

- Intravenous fludarabine for second line therapy
- Oral fludarabine for second line therapy
- Intravenous fludarabine for salvage therapy
- Oral fludarabine for salvage therapy

2 There are four sources of data for cost effectiveness data and/or analysis.

- A Wessex Institute DEC report (1995)
- Schering (manufacturer's submission)
- Roche (manufacturer's submission ***for rutiximab for follicular non-Hodgkin's lymphoma***).
- The CLL3 trial conducted by the MRC collected data on side-effects of fludarabine.

3 The DEC report

- The problems with the DEC report are numerous:
  - It is now an old report, and the cost of the drug has changed
  - The incremental utility gain of 0.11 for fludarabine and of 0.02 for CHOP are little better than guesses. It seems to be felt that the utility gain for fludarabine is somewhat too high.
- The estimated cost per QALY for iv fludarabine compared with no treatment, from the DEC report, is given as £64,000, but with the present cost for iv fludarabine, the cost per QALY compared with no treatment falls to £55,000. Using this methodology and substituting the cost of oral fludarabine, the cost per QALY falls to £34,000.
- The estimated cost per QALY for fludarabine compared with CHOP is lower than compared with no treatment (since CHOP against no treatment is less cost-effective than fludarabine against no treatment). It is estimated for iv fludarabine as £45,000 at the old price, £35,000 at the current price and for oral fludarabine, £9,000.

4 The Schering submission

- This analysis involved only 17 patients for fludarabine and 5 for CHOP

- For second line therapy, the following costs and benefits pertain
    - The “expected” time in remission for fludarabine was 155 days, and for CAP was 48 days, taken from an RCT. (It is not clear whether “expected” refers to median or mean.) It is ***assumed*** that the expected time in remission for CHOP is the same as for CAP. (It is also not clear whether the 155 days expected time in remission refers only to the 48% of patients who responded to fludarabine or is averaged over all patients. If it is a median, it must refer to the 48% of responders only.) Similarly for the 27% who responded to CHOP.
    - Thus, the benefits of fludarabine are given as an incremental 107 days of remission
    - The costs are given in the following table. From the experience of the 17 fludarabine and 5 CHOP patients, it is assumed that only 4.1 out of 6 cycles of fludarabine and 3.6 out of 6 cycles of CHOP are given. (This set of assumptions is changed later.)

Treatment	**fludarabine iv**	**fludarabine oral**	**CHOP**	**CAP**
Source	patient audit, expert panel, BNF			
Costs				
Acquisition cost of drug	£2,665	£2,665	£753	£637
Cost of administration	£2,617	£299	£1,101	£1,101
Cost of prophylaxis	£114	£114	£142	£142
Cost of monitoring	£369	£369	£300	£300
Cost of adverse events	£267	£267	£632	£632
Total cost	**£6,032**	**£3,714**	**£2,928**	**£2,813**

Incremental cost effectiveness: this is taken from table 8 of Schering’s submission, except that it is extended to include incremental iv fludarabine against CHOP.

Treatment	**Fludarabine iv**	**fludarabine oral**	**CHOP**	**Incremental (fludara iv-CHOP)**	**Incremental (flud oral-CHOP)**
Cost of therapy	£6,032	£3,714	£2,928	£3,104	£786
Effectiveness (disease-free days)	155	155	48	107	107
Cost per year of remission	£14,204	£8,746	£22,265	£10,600	£2,681

This shows that the incremental cost per year of remission compared with CHOP is £10,600 for fludarabine given intravenously and £2,700 for fludarabine given orally. If the utility gain for fludarabine is 0.11 and for CHOP is 0.02 during that year of remission (using the Wessex DEC estimate, for the sake of comparison) and there is no survival advantage for fludarabine or CHOP, then the incremental cost per QALY for iv fludarabine compared with CHOP is £118,000, and is £30,000 for oral fludarabine.

5 The Roche submission for rituximab

- This is a comparison for a different disease. In some ways, this should not matter, because unless side effects are caused ***because the drug interacts with the condition***, the effect of the drug on the patient should give the same side-effects whatever the condition. However, it is likely that the general health-state of the patient could change the extent of the side-effects. A group of patients who are all in a poor health state are likely to be more severely affected by side-effects than a group whose patients are in a better state.

- That caveat aside, the Roche submission estimates that fludarabine has much greater side effects than does the Schering (manufacturer) submission. In the Schering submission, the 17 patients had what appears to be 11 inpatient hospital days in six months, equal to 0.65 inpatient days per patient, due to side effects of fludarabine. The 50 patients from the Roche submission, taken from work performed by Foran (2000), had what seems to be 342 inpatient days, or 6.84 days per patient. (This is derived as 57 days from cycle 3 of 6 cycles, multiplied by 6 to account for the 6 cycles.) The discrepancy between this relatively high figure and that of Schering's (= 0.65 inpatient days per patient) is apparently not due to patients being admitted to hospital for other reasons, because those patients in the Roche submission who were prescribed rituximab had virtually no inpatient days. However, as stated in the paragraph above, the "Roche patients" may have been in a poorer health state than the "Schering patients". The Roche data follows in tabular form.

Total Direct Treatment Costs (£)

	CHOP	Fludarabine	Rituximab
Cost administration inpatient	334	802	371
Cost administration outpatient	755	2,976	424
Drug acquisition cost	960	3,900	4,890
Cost adverse events	5,802	3,540	119
Cost of tests	892	590	741
Total per patient per course	8,744	11,808	6,544

The relativity of adverse event costs of fludarabine and CHOP is maintained by the Roche estimates, as Roche's adverse event costs for CHOP are also much higher than for the Schering submission. Costs of hospitalization for fludarabine were £2,327, or 65% of the total cost of adverse events of fludarabine.

6. Comparison of Schering and Roche data

- Roche's patients were assumed to take the full 6 cycles of fludarabine and CHOP. To compare the analyses, we convert Schering's costs from those based on 4.1 treatment cycles to 6 (for fludarabine) and from 3.6 to 6 (for CHOP). The following table shows the comparison of costs.

	Roche		**Schering**		
	Fludarabine(iv)	CHOP	Fludarabine (iv)	CHOP	Flud (oral)
Administration	3778	1089	3738	1384	427
Drug cost	3900	960	3900	1254	3900
Adverse events	3540	5802	559	1293	559
Tests	590	892	540	500	540
Total costs	11,808	8,743	8,737	4,431	6,426

- It is apparent that the costs in the two analyses are very similar, except for side-effects. We now see how the Schering analysis would change if we put the Roche costs into the analysis.

Treatment	**Fludarabine iv**	**fludarabine oral**	**CHOP**	**Incremental (fludara iv-CHOP)**	**Incremental (flud oral-CHOP)**
Cost of therapy	£11,808	£8,797	£8,743	£3065	£54
Effectiveness (disease-free days)	155	155	48	107	107
Cost per year of remission	£27,800	£20,700	£66,500	£10,500	£200

- Because the adverse events associated with fludarabine and CHOP are increased by about the same amount (actually slightly more for CHOP), the incremental cost effectiveness of intravenous fludarabine against CHOP is virtually unchanged from the previous analysis, but for oral fludarabine it is reduced almost to zero.

7. Other evidence

- Unpublished data, from non responders to first-line chemotherapy, from the MRC's CLL3 trial, show that of 87 patients on fludarabine over a six-month period, 10 spent up to a week in hospital, 21 spent between a week and a month, and 6 spent over a month. On the basis that the first group averaged 3 days, the second group 12 and the third group 40 days, the average duration of stay for the 87 patients was 6.0 days. This suggests that the Roche estimates of side effects for fludarabine may be closer than the Schering estimates. However, the cost of adverse events was not distinguished from the cost of treating the disease in this analysis, so the result obtained in the sentence above cannot be relied upon. The same is true for blood transfusions, for which there was an average of about one per patient over the six months, somewhat higher than the Schering estimates.

- In QALY terms, if the utility gain for the 155 days free of disease is 0.11 with fludarabine and for the 48 days of CHOP is 0.02, then the estimated QALY difference is 0.044. Thus, the incremental cost per QALY for intravenous fludarabine compared with CHOP is £3065/0.044 = £69,500 for intravenous but only £54/0.044 = £1,200 for oral.

8. Summary

The evidence is poor. The DEC evidence is relatively old and based on questionable utility figures. The Schering evidence is based on very small sample sizes and therefore subject to large sampling error. In particular, the cost of adverse events is suspect. The Roche analysis has been performed to show rituximab to advantage, so it may also be subject to bias.

If the cost of adverse events for fludarabine and CHOP are of similar magnitude, as they happen to be in both Schering's and Roche's submissions, then oral

fludarabine is seen to be cost effective on the analysis presented. (Intravenous fludarabine, however, is probably not cost effective.) However, if the true cost of adverse events for fludarabine is greater than for CHOP, then oral fludarabine may not be cost effective.

Given the present level of evidence, which subjects the results to a great deal of uncertainty, it would appear that CHOP is not cost effective against oral fludarabine or against no treatment. Oral fludarabine compares well with a treatment (CHOP) that is not cost-effective, so in itself that should only be of consequence if CHOP were to be given if fludarabine were not available. If CHOP (or any other drug) were not to be given, then fludarabine would be used simultaneously as second line and salvage treatment. Against no treatment, intravenous fludarabine is probably not cost effective, but oral fludarabine (if it can reliably provide the same bio-availability as intravenous fludarabine) is more likely to be cost effective. The cost for a remission-free year according to Schering is £8,700 but with the greater cost of side-effects (using Roche's data) is estimated to be £20,700. The cost per QALY, based on a utility gain during remission of 0.11, is about nine times these figures.