For committee, projector, public

Lead team presentation Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) for treating pancreatic cancer after gemcitabine [ID778]

1st Appraisal Committee meeting

Background and Clinical Effectiveness

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27 July 2016

Disease background

- 10th commonest cancer 3% cancer cases; UK 9,408 people diagnosed in 2013
- Mean age: 71 men 75 women
- Poor outcomes
  - Median survival post diagnosis 4.6 months
  - 21% survive 1 year, 3% 5 years, 1% 10 years
  - Few patients (10-20%) suitable for curative surgery
  - 53-88% of people suitable for surgery have a recurrence
- Patients often present late when disease already spread locally or metastasized
- Symptoms include pain, jaundice, weight loss, depression, anxiety

Treatment pathway

First-line

- Surgery (10-20% patients eligible)
- Gemcitabine if patient meets criteria* (TA25)
- FOLFIRINOX (Folinic acid, 5FU, Irinotecan, Oxaliplatin)

Subsequent treatment

- Folinic acid, 5FU, oxaliplatin regimens (mFOLFOX 4 and 6 and OFF)
- 5-FU/LV
- Capecitabine +/- oxaliplatin

*only if the person has a Karnofsky performance score of 50 or more and potentially curative surgery is not a suitable treatment.

Patient perspectives (1)

- On average 21% survival rate at 12 months
- High proportion of those diagnosed 75yrs+
- Surgery only hope of a cure
  - Surgery not an option for many due to stage at diagnosis
- No recognised standard of care / licensed treatment options after gemcitabine
- Devastating diagnosis

Patient perspectives (2) - desired treatment outcomes

- Extended overall survival
- Controlled side effects
- Treatment options

Concerns about treatment with nal-iri+5FU/LV

- Little knowledge of drug in UK

Innovation?

- ‘Does the drug bypass the stroma to deliver direct to tumour’?*

*this point has been updated in line with a factual error raised at the committee meeting

Treatment being appraised

- Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri); brand name Onivyde
- Received positive CHMP opinion on 21 July 2016:
  - 'Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy'
- Intravenous infusion in combination with 5-FU and folinic acid (leucovorin; LV)
- Dosage – treatment until disease progression (average 8 cycles in NAPOLI-1 trial)
  - Nal-iri 80 mg /m ^{2} over 90 minutes
  - LV 400 mg/m ^{2} over 30mins followed by 5-FU 2400 mg/m ^{2}
- Mechanism of action
  - Blocks DNA enzyme topoisomerase 1
  - Company says nano particles result in more delivery of drug to tumour, less peripheral conversion to active metabolites in plasma systemically and more active drug / metabolite in tumour
  - No clinical data supporting more clinically active that non nanoparticle irinotecan

NICE scope and company's decision problem

	NICE scope	Company
Population	People with metastatic adenocarcinoma of the pancreas that has been treated with gemcitabine-based treatments	
Intervention	Nal-iri +5-FU/LV	
Comparator(s)	• Oxaliplatin + 5-FU/LV • Oxaliplatin + capecitabine • Fluoropyrimidine monotherapy	• 5-FU/LV • Oxaliplatin + 5-FU/LV (indirect comparison for cost analyses)
Outcomes	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	

NAPOLI-1 trial: direct comparison of nal-iri + 5-FU/LV with 5-FU/LV

- Only direct trial evidence
- Greater proportion of patients received prior gemcitabine combination therapy (54.2%) and fewer gemcitabine monotherapy (45.8%)
  - Monotherapy more common in NHS practice
- Patients underwent testing for UGT1A1 genotype (associated with irinotecan toxicity) and had dosage reduced if detected
  - Not current NHS practice
- Randomisation stratified by albumin level, ethnicity and Karnofsky performance score
- Primary endpoint: overall survival
- Secondary endpoints
  - Progression free survival, time to treatment failure, objective response rate, tumour marker response and clinical benefit

NAPOLI-1 trial results (1)

- Overall survival: Median 6.1 months nal-iri + 5-FU/LV compared with 4.2 months for 5-FU/LV; p=0.0122 (data cut-off February 2014)
  - May 2015 cut-off; 6.2 months (95% CI: 4.8 to 8.4) for nal-iri plus 5-FU/LV compared with 4.2 months (95% CI: 3.3 to 5.3) for 5-FU/LV
- Progression-free survival (ITT population) greater for nal-iri+5-FU/LV than 5-FU/LV group
  - 3.1 months (95% CI: 2.7 to 4.2) compared with 1.5 months (95% CI: 1.4 to 1.8); p=0.0001
- Median TTF (ITT population) was statistically significantly longer for nal-iri plus 5-FU/LV compared with 5-FU/LV
  - 2.3 months compared with 1.4 months; p=0.0002

NAPOLI-1 trial results (2): Quality of life

- EORTC-QLQ-C30
  - Cancer specific questionnaire
- Measured at start of treatment, every 6 weeks and 30 days post follow up
- Analysed ITT baseline and at least one follow up
- Nal-iri 5FU/LV n=71 5FU/LV n= 83
- Results at 6 weeks and 12 weeks showed no real differences suggesting no negative effect on health-related quality of life
- To support evidence company carried out a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis:
  - nal-iri+5-FU/LV patients had a 1.3 months (95% CI: 0.4 to 2.1) greater Q-TWiST with a relative Q-TWiST gain of 24%

NAPOLI-1 trial results (3): Adverse events

- 95% included in safety analysis (n=398)
- Duration of exposure to drug 15 weeks in nal-iri +5FU/LV and 10.4 weeks for 5FU/LV
  - proportion experiencing a treatment emergent adverse event (TEAE) was similar in both groups
  - experience grade 3 or worse events; 77% in nal-iri 5-FU/LV and 56% in 5-FU/LV and nearly all experience at least 1

Company's indirect treatment comparison (ITC)

- No direct trial evidence for comparison between nal-iri+5FU/LV and oxaliplatin+5FU/LV
- The company considered that there were no suitable trials to carry out an ITC to assess clinical efficacy between nal-iri+5F/LV and oxaliplatin+5FU/LV
  - However company carried out ITC for cost-effectiveness analysis resulting in a hazard ratio of 0.7 for PFS and 0.63 for OS

Evidence Review Group's critique (1)

- NAPOLI-1 trial:
  - Not blinded and no independent assessment of disease
  - Comparator 5-FU/LV rarely used in clinical practice
  - Greater proportion of people received prior gemcitabine combination therapy than seen in clinical practice in UK
  - High proportion of patients received therapy after study in both arms – affect on OS?
    - Subsequent treatments received in both groups fairly balanced
  - Greater number in the 5-FU/LV group did not receive treatment than in nal-iri+5-FU/LV group

Evidence Review Group's critique (2)

- Other issues:
  - Oxaliplatin+5FU/LV most appropriate comparator
  - ERG's indirect comparison of clinical data:
    - When considering trials that could have been included, OS for oxaliplatin+5-FU/LV between 5.9 and 6.7 months
    - OS similar to nal-iri+5-FU/LV in NAPOLI-1 trial (6.1 month)
    - Safety data - more neutropenia and neurotoxicity with oxaliplatin+5FU/LV and more diarrhoea with nal-iri+5FU/LV*
  - Issues with indirect comparison
    - Different trial populations
    - Different oxaliplatin+5-FU/LV regimens in trials
    - Survival data not comparable – proportional hazards not valid
  - Unsure if Q-TWiST was post-hoc analysis

*this point has been updated in line with a factual error raised at the committee meeting

Key issues for consideration

Generalisability	Is the NAPOLI-1 trial generalisable to the UK?
Most suitable comparator	• 5FU/LV was the comparator used in NAPOLI-1. Is 5FU/LV ever used in NHS practice? • Clinical advice to the ERG suggested Oxaliplatin + 5FU/LV is the most relevant comparator in NHS practice • Capecitabine +/- oxaliplatin?
Indirect comparison	Are the HRs from the ITC with Oxaliplatin+5FU/LV reliable for decision making?
ERG literature review	Suggested that PFS/OS results for Oxaplatin+5FU/LV were similar to those reported in NAPOLI-1. Do the clinical experts agree?