Review of:
TA100: Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer

This guidance was issued in April 2006

TA100 is currently on the list of static guidance and therefore does not have a specified review date.

Recommendation

- TA100 should be incorporated in the on-going clinical guideline. That we consult on the proposal.

Consideration of options for recommendation:

Options	Yes / No	Comment
A review of the guidance should be planned into the appraisal work programme.	No	Since TA100 was published, the licence for capecitabine has been extended to include combination therapy, in addition to the existing indication in TA100 of monotherapy. However, Topic Selection confirmed that combination therapy was not considered to be an important topic, as it was already naturally filtered into clinical practice indicating that there was no clinical uncertainty.
The decision to review the guidance should be deferred	No	See above. TA100 is currently on the static list and not enough evidence has been identified to warrant an update of the guidance.
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	No	There are no existing treatments for the adjuvant treatment of stage III (Dukes' C) colon cancer that have been appraised by NICE and are due for review in the near future. Irinotecan for the adjuvant treatment of colon cancer is currently suspended until further progress is made on licensing timelines.
A review of the guidance should be combined with a new appraisal that has recently been referred to	No	There are no new treatments for the adjuvant treatment of stage III (Dukes' C) colon cancer that have been referred to NICE for appraisal

the Institute.		in the near future. The other treatments that have been reviewed by the topic selection panel have been for the treatment of metastatic colorectal cancer and are therefore not relevant to this appraisal.
A review of the guidance should be incorporated into an on-going clinical guideline.	Yes	TA100 is currently on the static list and not enough evidence has been identified to warrant an update of the guidance, either through a re-appraisal or through an on-going clinical guideline. It is therefore recommended that TA100 is incorporated into an on-going clinical guideline with mention of the licence extension for capecitabine to include combination therapy.
A review of the guidance should be updated into an on-going clinical guideline.	No	As above.
A review of the guidance should be transferred to the 'static guidance list'.	No	This option would not be appropriate due to the change in the licensed indication for capecitabine.

Original remit

TA100: *"To appraise the cost and clinical effectiveness of the use of oxaliplatin, irinotecan and capecitabine as adjuvant therapy in colorectal cancer."*

Current guidance

TA100:

1.1 The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition:

- capecitabine as monotherapy
- oxaliplatin in combination with 5-fluorouracil and folinic acid.

1.2 The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.

Relevant Institute work

Published

Improving outcomes in colorectal cancer. Cancer service guidance CSGCC. Published: June 2004. Review date: not specified.

Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer (review of TA33). Technology Appraisal TA93. Published: August 2005. To be incorporated in the ongoing colorectal cancer Clinical Guideline.

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Technology Appraisal TA118. Published January 2007. Review scheduled for July 2010.

Laparoscopic surgery for the treatment of colorectal cancer. Technology Appraisal TA105. Published: August 2006. Static guidance. Due to be incorporated in the ongoing colorectal cancer Clinical Guideline.

In progress

Diagnosis and management of colorectal cancer. Clinical Guideline. Expected publication date: October 2011.

Panitumumab in combination with chemotherapy within its licensed indication for the treatment of metastatic colorectal cancer. Technology Appraisal. Expected publication date: TBC.

Cetuximab, bevacizumab and panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first line chemotherapy (review of technology appraisal 150 and part-review of technology appraisal 118). Technology Appraisal. Expected publication date: TBC.

Suspended/terminated

Irinotecan for the adjuvant treatment of colon cancer. Technology Appraisal. Expected publication date: Suspended in 2005 until further progress is made on licensing timelines.

Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy. Technology Appraisal TA150. Due: June 2008. Appraisal terminated as no evidence submission was received from the manufacturer.

In topic selection

[redacted]

[redacted]

Safety information

Capecitabine: SPC updated in May 2010 with more data on adverse reactions (source: NeLM).

Recruitment to the AVANT trial of capecitabine, in combination chemotherapy with or without bevacizumab in treating patients who have undergone surgery for stage II or III colon cancer, was temporarily suspended in 2006 due to safety concerns (source: NeLM).

Details of changes to the indications of the technology

Drug (manufacturer)	Details
Capecitabine (Roche)	The indication considered in TA100 – monotherapy for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer – has also been widened to allow for use in combination with other drugs. Capecitabine is also licensed in certain circumstances for breast and gastric cancers
Oxaliplatin (Generic)	No change

Details of new products

Drug (manufacturer)	Details
Colorectal cancer vaccine (autologous tumour cell vaccine) (Vaccinogen)	Phase III. UK launch planned 2012.
Aflibercept (Sanofi Aventis)	Phase III as second-line combination therapy. UK launch planned Q2 2012.
MVA-5T4 (Oxford Biomedica)	Phase II as first line, combination therapy.
Panitumumab (Takeda)	Launched as third line monotherapy, Phase III as first and second-line monotherapy.
Perifosine (Keryx)	Phase III for advanced or metastatic colorectal cancer. UK launch not anticipated for >5 years.

On-going trials & unpublished

Trial name	Details
Follow up to MOSAIC study - A non-interventional follow-up to the MOSAIC study (multicenter international study of oxaliplatin/5-Fluorouracil/leucovorin in the adjuvant treatment of colon cancer) up to 10 years, and translational research	Open for recruitment Closure date: March 2012
A Study of Xeloda (Capecitabine) Plus Oxaliplatin in Patients With Colon Cancer	Ongoing Estimated completion date: December 2011
Study Investigating the Role of Oxaliplatin Duration in Modified FOLFOX-6 Regimen as Adjuvant Colon Cancer Therapy	Currently recruiting Estimated primary completion date: December 2012 Estimated study completion date: December 2016
SCOT - Short Course Oncology Therapy : a study of adjuvant chemotherapy in colorectal cancer by the CACTUS and QUASAR 3 Groups	Ongoing Estimated completion date: April 2012
A Study of Xeloda (Capecitabine) Compared With 5-Fluorouracil in Combination With Low-Dose Leucovorin in Patients Who Have Undergone Surgery for Colon Cancer	Completed (circa March 2008)

FOCUS 2: Drug treatment for bowel cancer - making the best choices when as milder treatment is needed	Completed (2007) – involves reduced dose versions of standard regimens.
PACT (Patient Preferences in Adjuvant Colorectal Cancer Therapy): a randomised crossover clinical trial comparing Bolus Fluorouracil/Leucovorin to Capecitabine as treatment for moderate to high risk resected colorectal cancer	Completed in 2006

Proposal for updating the guidance

If the guidance is to be updated as an appraisal, it would be scheduled into the work programme accordingly.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2009 (the date of the previous review proposal) onwards were reviewed. The results of the literature search are discussed in the 'Appraisals comment' section below.

Implementation

A submission from Implementation on TAs 100 and 176 (which is considered in a separate paper) is attached at the end of this paper.

On reading the implementation report, it is unclear to what extent TA100 is being adhered to as capecitabine and oxaliplatin are licensed in the UK for various indications.

Equality and diversity issues

In TA100, the Committee considered the fact that participants in trials for adjuvant treatment of stage III colon cancer are often younger than those who would be treated in clinical practice. It heard testimony from clinical experts that it is reasonable to extrapolate these results to older patients, that appropriately selected older people show a relatively good tolerability profile to the drugs, and that the effect on overall survival in those older people in

clinical practice is comparable with that seen in the younger trial participants. Additionally, the Committee heard evidence from the Assessment Group that, if an older cohort of people was used in the model that was more representative of the population under consideration, and survival benefits for this group were assumed to be equivalent to those for the group of trial participants, the cost-effectiveness estimates would not materially change.

Appraisals comment:

The licence for capecitabine in this indication has been extended since TA100 was published. TA100 recommended capecitabine as monotherapy and oxaliplatin in combination with 5-fluorouracil and folinic acid as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery. At that time capecitabine was licensed for 'the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer' and oxaliplatin in combination with intravenous 5-FU/FA was licensed for adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour. Capecitabine is still licensed in the UK for 'the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer' but the Summary of Product Characteristics includes combination treatment. According to the Summary of Product Characteristics, data from one multicentre, randomised, controlled phase 3 clinical trial in patients with stage III (Dukes' C) colon cancer currently supports the use of capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968 study) and a meta-analysis of six clinical trials (studies SO14695, SO14796, M66001, NO16966, NO16967, M17032) supports capecitabine replacing 5-FU in mono- and combination treatment in gastrointestinal cancer (colon, colorectal and advanced gastric cancer). However, Topic Selection has confirmed that combination therapy in this indication was not considered to be an important topic, as it was already naturally filtered into clinical practice, indicating that there was no clinical uncertainty.

No new technologies have been referred to NICE for appraisal in stage III (Dukes' stage C) colon cancer and no existing guidance is due in this indication for review. Any new technologies or reviews of existing guidance in this therapeutic area refer to metastatic disease.

In TA100, the Committee cited uncertainty with regards to utility values and the indirect comparison between oxaliplatin plus 5-FU/FA and capecitabine. Research recommendations included comparisons of the effectiveness, tolerability, acceptability to patients and costs of the different oxaliplatin plus 5-FU regimens in the adjuvant setting (particularly those that combine oxaliplatin with oral forms of 5-FU), optimum duration of adjuvant therapy and detailed resource data and health-related quality of life data, especially those related to adverse events. The MOSAIC ten-year follow up study is still recruiting until March 2012 and a Chinese study of two modified FOLFOX-6 regimes is due to complete in December 2012. These studies do not appear, from the available information, to be collecting health-related quality of life or resource data and it is uncertain to what extent the Chinese study would address the uncertainties in TA100.

In conclusion, there appears to be no new evidence that could potentially change the recommendations in TA100.

Key issues

Since TA100 was published, the licence for capecitabine has been extended to include combination therapy, in addition to the existing indication in TA100 of monotherapy. However, Topic Selection confirmed that combination therapy was not considered to be an important topic, as it was already naturally filtered into clinical practice indicating that there was no clinical uncertainty. There is no new evidence to suggest that an update of this appraisal is needed at this stage and we therefore recommend that this appraisal is incorporated into the guideline

GE paper sign off: Elisabeth George 23 03 11

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION PROGRAMME

Guidance Executive Review

Technology appraisal TA: 100/176: Colorectal cancer (first line, adjuvant) - capecitabine, tegafur uracil, oxaliplatin, cetuximab

1. Routine healthcare activity - IMS HEALTH Hospital Pharmacy Audit Index (HPAI)

This section provides information on prescribing cost and volume for drugs issued in hospitals in England. The data are obtained from the IMS HEALTH Hospital Pharmacy Audit Index. All costs stated in this report are based on estimated cost.

1.1 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – capecitabine

Figure 1 Trend in the cost of prescribing capecitabine in hospitals in England

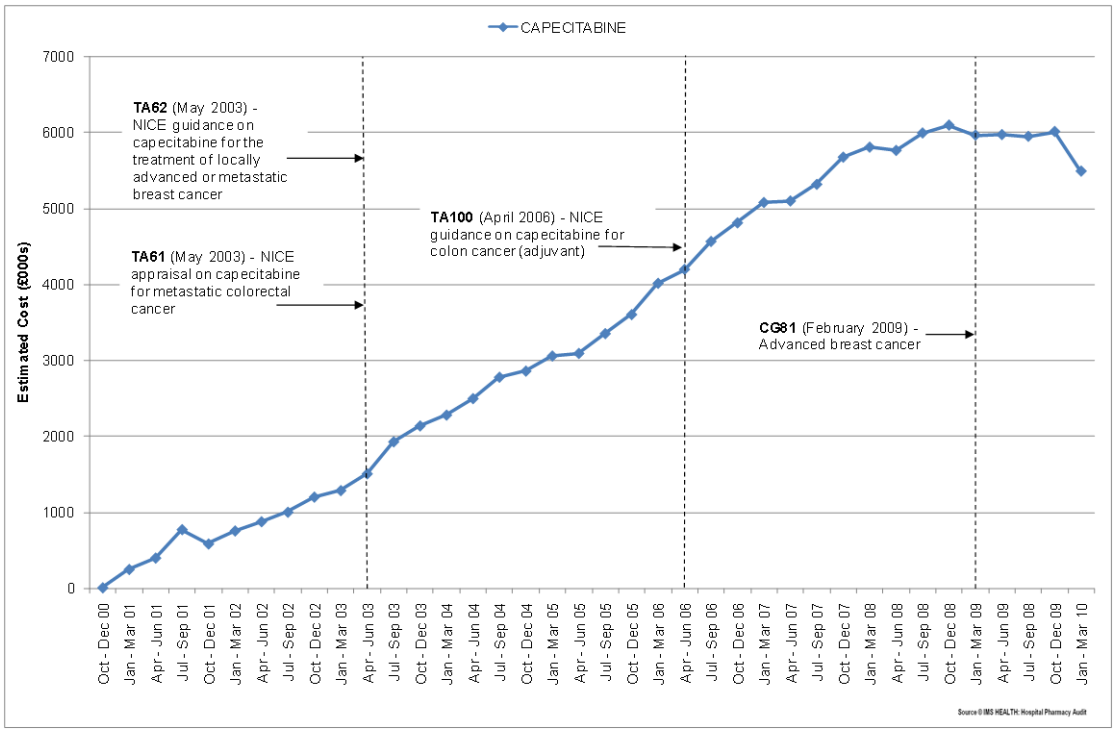
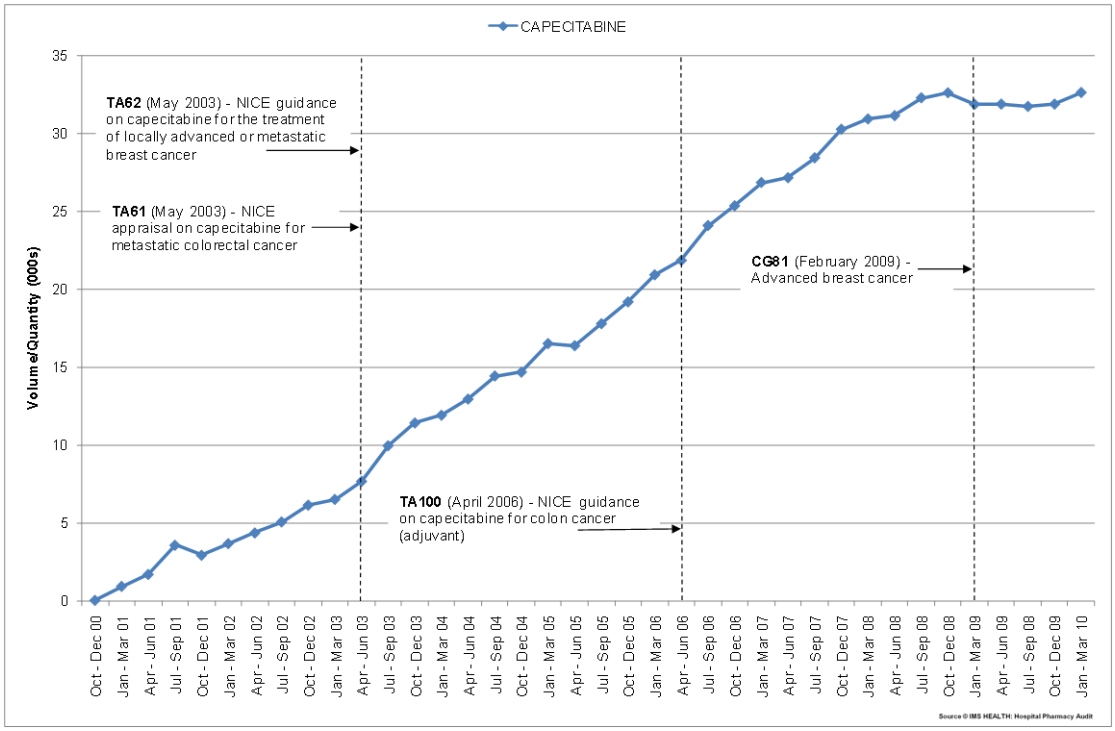


Figure 2 Trend in the volume of prescribing capecitabine in hospitals in England



The above charts show that following the publication of NICE technology appraisal 100 (and other related appraisals), the prescribing costs and volume for capecitabine continued to increase. In the quarter January to March 2006, prior to the publication of NICE technology appraisal 100, the costs were £4,011,083. By January to March 2009 the estimated costs had reached £5,962,059. In the quarter January to March 2010, the estimated costs dropped to £5,488,679. However prescribing volume did not follow the same pattern and has remained around 31,000 items since the first quarter of 2009. This fall in costs during the final quarter of 2009/10 could be for a number of reasons but the continuing level of prescriptions at the same time suggests a change in prescribing behaviour to using smaller pack sizes or dosages. It is unclear yet whether this is a temporary or ongoing trend.

This data must be interpreted with caution and cannot necessarily be attributed to increases in prescribing for colon cancer as data do not link to diagnosis.

1.2 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – oxaliplatin

Figure 3 Trend in the cost of prescribing oxaliplatin in hospitals in England

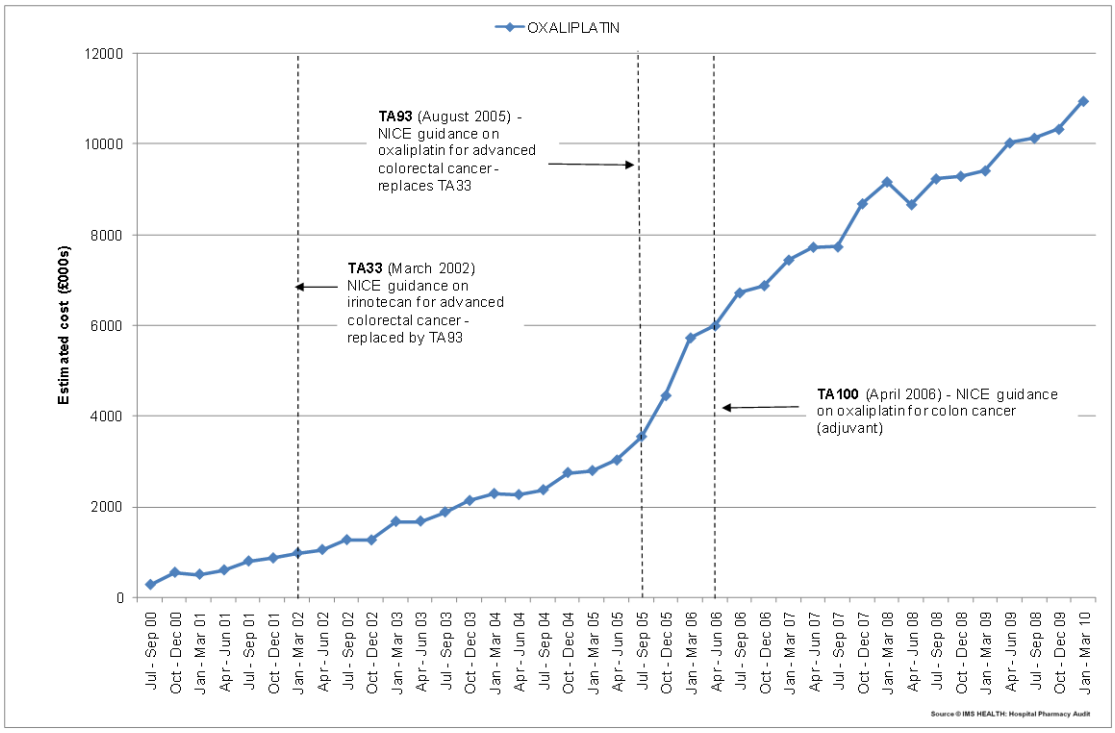
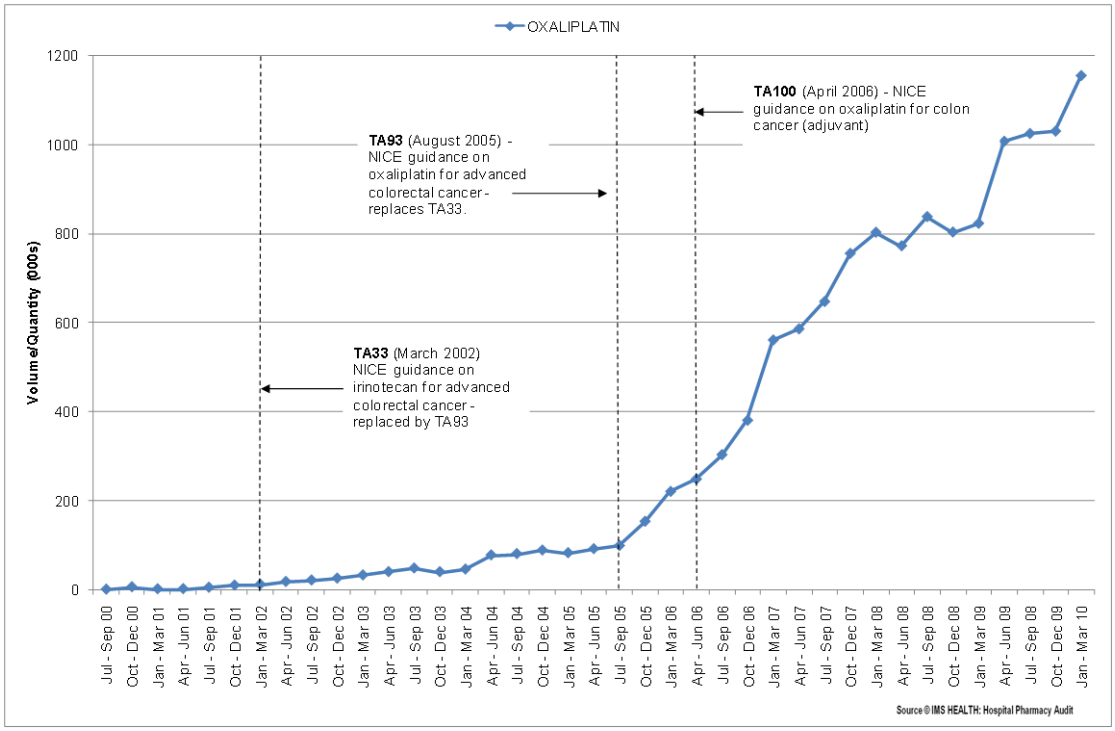


Figure 4 Trend in the volume of prescribing oxaliplatin in hospitals in England

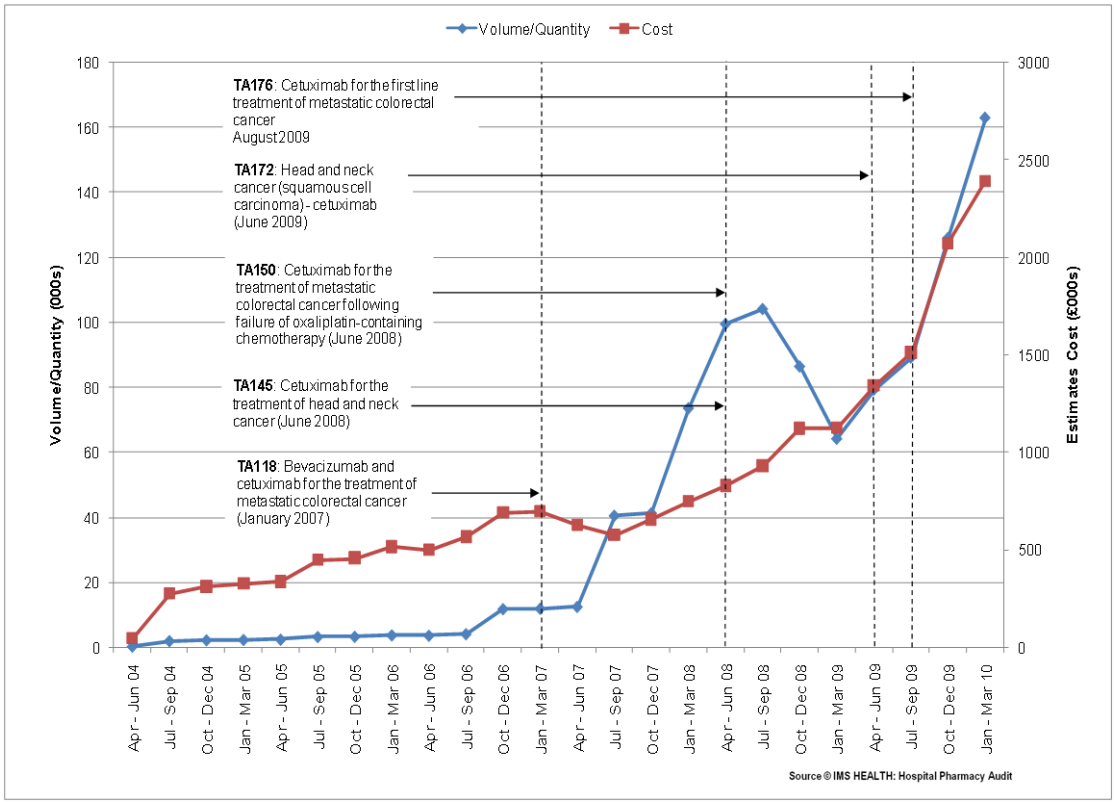


The above charts show that following the publication of NICE technology appraisal 100 (and other related appraisals) the prescribing costs and volume for oxaliplatin continued to increase. In the quarter January to March 2006 prior to the publication of NICE guidance, the costs were £5,723,986. By January to March 2010 the estimated costs had reached £10,951,995. The slight discrepancies between the trends on the graphs for cost and volume may be related to the availability and use of different vial sizes and generic versions.

This data must be interpreted with caution and cannot necessarily be attributed to increases in prescribing for colon cancer as data do not link to diagnosis.

1.2 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – cetuximab

Figure 5 Trend in the cost and volume of prescribing cetuximab in hospitals in England



The above chart shows that the costs of prescribing cetuximab have increased consistently over the period to March 2010. The volume/quantity has however fluctuated. This may potentially be in response the outcomes of NICE appraisal decisions. It is not possible to be certain why the trends in volume/quantity and costs do not mirror each other but this may be due to trends in the availability and use of different sized vials.

Notes:

- The IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI) collects information from pharmacies in hospital trusts in the UK. The IMS HPAI database is based on 'issues' of medicines recorded on hospital pharmacy systems. 'Issues' refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.
- Volume/Quantity: This is the number of packs of a medicine that are issued. They should not be added together due to differences in dosages/pack sizes.
- Cost (in £s): Estimated costs are calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost. Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.
- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of packs used, although it does not account for patients receiving different dosages or durations.
- Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.

2.1 Department of Health (2009) Uptake of NICE approved cancer drugs 2007/2008 London: Department of Health

An analysis of prescribing data across cancer networks. Data show a 73% increase in prescribing of capecitabine from 2005 to 2007/08 and a 28% reduction in variation across networks; a 179% increase in prescribing of oxaliplatin from 2005 to 2007/08 and a 23% reduction in variation across networks (NB data is not linked to diagnosis).

Tegafur/uracil was excluded from this study as low usage prevents meaningful comparisons of median usage and variation