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TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

**CellSearch[®]: detection of circulating tumour
cells for the prognosis and improved
management of cancer patients**

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PRIORITISING SUMMARY

REGISTER ID: 000487

NAME OF TECHNOLOGY: CELLSEARCH[®] CIRCULATING TUMOUR CELL TEST

PURPOSE AND TARGET GROUP: DETECTION OF CIRCULATING TUMOUR CELLS FOR PROGNOSIS DETERMINATION AND IMPROVED MANAGEMENT OF CANCER PATIENTS

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input type="checkbox"/> Yet to emerge | <input checked="" type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|--|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input type="checkbox"/> No | |
| <input checked="" type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

| COUNTRY | LEVEL OF USE | | |
|-------------|------------------------------|-------------|-----------------|
| | Trials Underway or Completed | Limited Use | Widely Diffused |
| USA | ✓ | | ✓ |
| UK | ✓ | ✓ | |
| Japan | ✓ | ✓ | |
| Netherlands | ✓ | | ✓ |
| Australia | | ✓ | |

IMPACT SUMMARY:

Veridex LLC (Raritan, NJ) provides CellSearch with the aim of detecting circulating tumour cells (CTCs) in the peripheral blood of cancer patients. The technology has recently emerged in Australia and is available at a multi-disciplinary clinic located within the Princess Alexandra Hospital, Brisbane. The clinic has a specific focus on prostate cancer management and research. CellSearch also has applications in the determination of prognosis and management of other cancers, particularly breast and colorectal cancers.

BACKGROUND

The principal determinant of cancer prognosis and management is the absence or presence of metastasis. One mechanism by which metastasis may occur is via CTCs in the peripheral blood.¹ These CTCs may be present even in patients who have no obvious evidence of metastasis after complete resection of a primary tumour and this is the basis for the subsequent development of overt metastases. The possible presence of CTCs in turn provides the justification for the current practice of systemic chemotherapy following definitive treatment of a primary tumour. However, despite continued improvements in chemotherapy, many patients are unresponsive to such treatment. There is a substantial amount of literature which suggests that monitoring CTCs enables early identification of patients responding to or failing therapy, allowing for earlier and more accurate prediction of the therapy's effectiveness, and as such, a comparison of CTC counts prior to, and after commencement of treatment, has the potential to improve management of cancer patients with a likelihood of metastasis (Lin et al 2010).

At present, the only system for CTC enumeration with FDA approval for routine clinical use in metastatic cancer patients is CellSearch[®]. The system operates by automatic enrichment and immunocytochemical detection of CTCs from peripheral blood. It consists of: CellSave preservative tubes which prevent CTC degradation for up to 96 hours; a pre-packaged kit for isolation and identification of CTCs; control cells for run-to-run quality assurance; CellTracks AutoPrep system for automatic addition of reagents to CellTracks Analyzer II, a semi-automated microscope for scanning and reading results (Van der Auwera et al 2010).

CLINICAL NEED AND BURDEN OF DISEASE

In 2006, the most recent year for which non-provisional Australian data are available, 104,592 new cases of cancer were diagnosed² (AIHW 2010). The age standardised incidence rate of 480 cases per 100,000 persons in 2006 was higher than the rate of 462 a decade earlier and much higher than the rate of 395 in 1986, which is a reflection of the growing cancer burden due to Australia's ageing population. It is projected that the number of new cancer cases in 2010 will be 115,000, which is a ten per cent increase compared to incident cases in 2006. In 2006 the average age at cancer diagnosis was 67 years for males and 64 years for females.

¹ Metastasis may also occur via the lymphatic system. Tumour cells which have reached the lymph nodes or bone marrow are known as disseminated tumour cells (DTCs).

² Excluding the two main types of non-melanoma skin cancer (basal and squamous cell carcinomas), which are the only cancers not routinely reported to the National Cancer Statistics Clearing House (NCSCH).

For males in 2006, prostate cancer was the most common incident cancer (excluding non-melanoma skin cancer), with 17,444 cases diagnosed³. Colorectal cancer (7,432 new cases) was the next most common cancer among males, followed by melanoma, lung cancer and lymphoma, with 6,051, 6,030 and 2,518 incident cases, respectively. These five cancer types accounted for 67 per cent of all cancers registered in males in 2006. In 2006, breast cancer (12,614 new cases) was the most commonly registered cancer in females. Colorectal cancer (6,159 new cases) was the second most common cancer among females, followed by melanoma, lung cancer and lymphoma, with 4,275, 3,533 and 1,961 incident cases, respectively. These five cancers accounted for 63 per cent of all cancers registered in females in 2006 (AIHW 2010).

Cancer is a major cause of death, accounting for 29 per cent of all deaths in 2007. Despite the age-adjusted death rate from cancer declining from 209 per 100,000 persons in 1987 to 176 in 2007 (a 16% decline), the total number of deaths is increasing given the ageing of the population. In 2007 there were 39,884 deaths from cancer. Of these, 22,562 were amongst males (32% of all male deaths) and 17,322 were amongst females (26% of all female deaths). The average age at death from cancer was 72 years for both sexes. Deaths from cancer in 2010 are projected at 43,700. Substantial declines in age specific death rates have occurred among the cancers which have been listed as national health priority areas, especially cervical cancer. Cancer deaths have also fallen steadily and substantially for colorectal, breast and lung cancers, 43, 28 and 17 per cent, respectively (AIHW 2010).

In 2007 a total of 19,736 new registrations of primary cancer were reported to the New Zealand Cancer Registry (MoH 2010). Males accounted for 10,425 (52.8%) of these while registrations for females numbered 9,311. Between 1997 and 2007 the actual numbers of new registrations increased from 16,135 to 19,736 (22.3%) while age-standardised rates, which adjust for age and population growth, decreased slightly over this period. In 2007, the age-standardised registration rate was 340.5 per 100,000 population (2.2% lower than the 1997 rate of 348.3).

There were 8,519 New Zealand deaths from cancer during 2007 (4,539 males and 3,980 females). This represents a 17 per cent increase in number of deaths from cancer in 1997. Conversely, age-standardised rates show that total cancer mortality decreased by 10.3 per cent over this ten-year period. The mortality rate for males in 2007 was 5.3 per cent higher than that in 2006, in contrast with the general declining trend observed since 1999. The female rate showed a downward trend and was 35.9 per cent lower than the male rate for 2007 (MoH 2010).

³ Rising incidence of prostate cancer in recent years is strongly associated with an increased use of prostate-specific antigen tests in screening for prostate cancer.

DIFFUSION

At present, one clinic within the Princess Alexandra Hospital in Brisbane uses CellSearch[®] for specialised management and research in prostate cancer.

COMPARATORS

Current practice in the monitoring of cancer progression and prognosis and managing/adapting cancer treatments involves radiographic imaging. Common modalities include CT and MRI. It is suggested that CTC enumeration may provide earlier indications of whether treatment is effective/appropriate and when changes, such as breaks in therapy and less aggressive regimens, are appropriate. Knowing when it is safe to administer lower levels or less frequent chemotherapy has important implications in terms of reducing toxic side-effects experienced by cancer patients.

SAFETY AND EFFECTIVENESS ISSUES

A prospective multicentre study enumerated CTCs in the peripheral blood of 430 patients (median age 64 years, range 22-92 years) with metastatic colorectal cancer (mCRC) using CellSearch[®] (Cohen et al 2008) (level II prognostic evidence). The study aimed to investigate the relationship of CTCs to treatment response, progression-free survival and overall survival. Patients were stratified into unfavourable and favourable prognostic groups based on CTC levels of ≥ 3 or < 3 CTCs per 7.5mL of blood, respectively. The threshold of three CTCs was selected following results from a training set of patients (n=109). Comparing outcomes from this training set and a validation set (n=321) showed no statistical differences and therefore the final study combined results for a total of 430 patients. Peripheral blood was obtained for CTC evaluation at baseline (prior to commencement of therapy) and four subsequent follow-up periods (1-2, 3-5, 6-12 and 13-20 weeks after therapy). All CTC evaluations were undertaken in one of four central laboratories with blinding to patient clinical status. The relationship of CTCs to treatment response, as indicated by radiographic imaging, was investigated and the possible prognostic role of CTCs was assessed by comparing favourable and unfavourable groups for progression-free and overall survival.

During the time of the analyses, a total of 202 (47%) patients died, and mean follow-up time for the remaining 228 patients was 12.6 ± 6.5 months. At baseline, 118 (26%) patients had unfavourable CTC levels and 384 (89%) had follow-up radiographic imaging after a mean of 9.2 ± 2.8 weeks. Twenty-eight (7%) did not have follow-up radiography and 18 (4%) died before follow-up imaging could be performed. Response to therapy (as indicated by radiography) versus CTC level (favourable or unfavourable) was assessed in 320 patients who had either undergone follow-up

imaging or died before imaging but had CTCs enumerated at three to five weeks⁴ (Table 1). Response to therapy was designated as either non-progressive or progressive disease. Non-progressive disease was defined as stable disease, partial response or complete response. Patients with progressive disease included those patients who died. CellSearch[®] was used to predict progressive disease as indicated by radiographic imaging with a sensitivity of 27 per cent (95% CI [17, 39]), specificity of 93 per cent (95% CI [89, 96]), positive predictive value of 53 per cent (95% CI [36, 69]), negative predictive value of 81 per cent (95% CI [76, 85]) and an overall agreement of 78% (95% CI [73, 82]).

Table 1 Response to therapy as indicated by radiographic imaging

| | CTCs 3-5 weeks after initiation of therapy | | | | | Total | % of Total |
|--------------------------------|--|----|--------------------------|----|-----|-------|------------|
| | <3 CTCs ("favourable") | | ≥3 CTCs ("unfavourable") | | | | |
| | No. | % | No. | % | | | |
| Non-progressive disease | 228 | 93 | 18 | 7 | 246 | 77 | |
| Progressive disease (or death) | 54 | 73 | 20 | 27 | 74 | 23 | |
| Total | 282 | 88 | 38 | 12 | 320 | 100 | |

Survival analysis found that patients with unfavourable CTC levels at baseline had significantly shorter progression-free survival than patients with favourable baseline levels, 4.5 months (95% CI [3.7, 6.3]) versus 7.9 months (95% CI [7.0, 8.6]), respectively (Figure 1). Similarly, overall survival was 9.4 months (95% CI [7.5, 11.6]) and 18.5 months (95% CI [15.5, 21.2]) for unfavourable and favourable groups, respectively (Figure 2). It was also observed that progression-free and overall survival were shorter at all time points for patients who had more than three CTCs per 7.5 mL of blood.

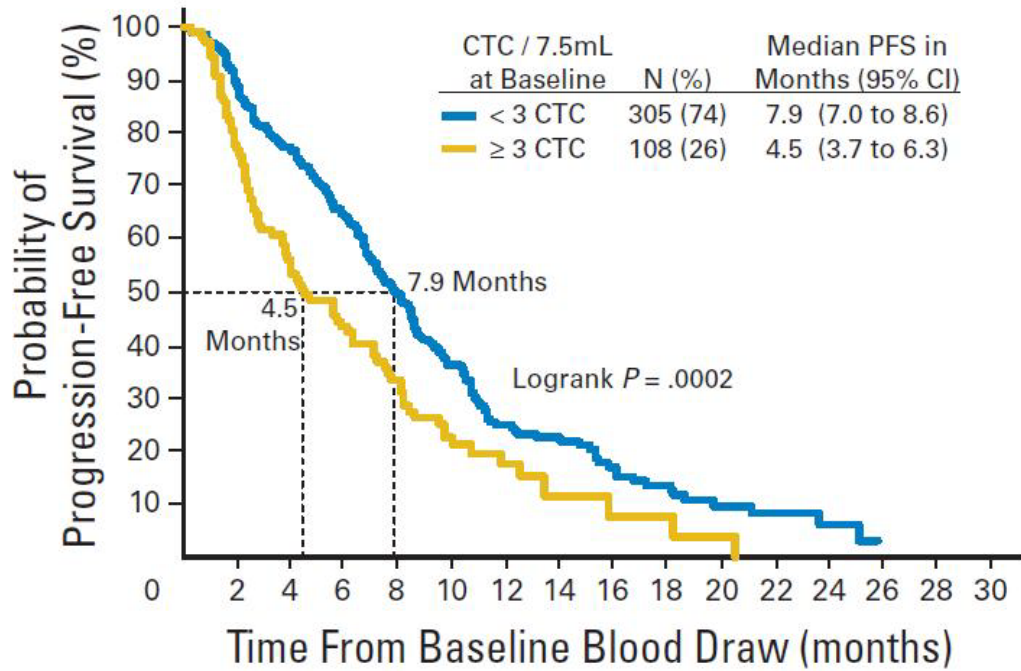
The relationship between change in CTC level from baseline to three to five weeks and clinical outcome was assessed in 319 patients, of whom four (1%) were excluded because they showed progressive disease prior to the three to five week follow-up. Progression-free survival was analysed for those patients for whom CTC count remained favourable (group 1), those who converted to favourable (group 2), those who converted to unfavourable (group 3) and those that remained unfavourable (group 4). Results are summarised in (Figure 2).

⁴ A total of 334 (78%) patients had CTCs enumerated at three to five weeks after initiation of therapy (mean 3.8 ± 0.7 weeks).

Table 2 Median progression-free survival by CTC status at baseline and 3-5 weeks

| Group | CTCs/7.5mL at baseline | CTCs/7.5mL at 3-5 weeks | n (%) | PFS, months [95% CI] |
|-------|------------------------|-------------------------|----------|----------------------|
| 1 | <3 CTCs | <3 CTCs | 226 (72) | 7.3 [6.0, 7.8] |
| 2 | ≥3 CTCs | <3 CTCs | 52 (16) | 6.2 [4.6, 7.0] |
| 3 | <3 CTCs | ≥3 CTCs | 9 (3) | 6.0 [0.5, NR] |
| 4 | ≥3 CTCs | ≥3 CTCs | 28 (9) | 1.6 [1.2, 2.7] |

PFS = progression-free survival; NR = not reported



| No. of patients at risk | |
|-------------------------|--|
| < 3 CTC | 305 269 229 187 138 88 44 32 20 15 8 6 3 0 0 0 |
| ≥ 3 CTC | 108 84 60 42 28 16 8 3 2 2 1 0 0 0 0 0 |

Figure 1 Probability of progression-free survival for favourable (<3 CTCs) and unfavourable (≥3 CTCs) patient groups (Cohen et al 2008).

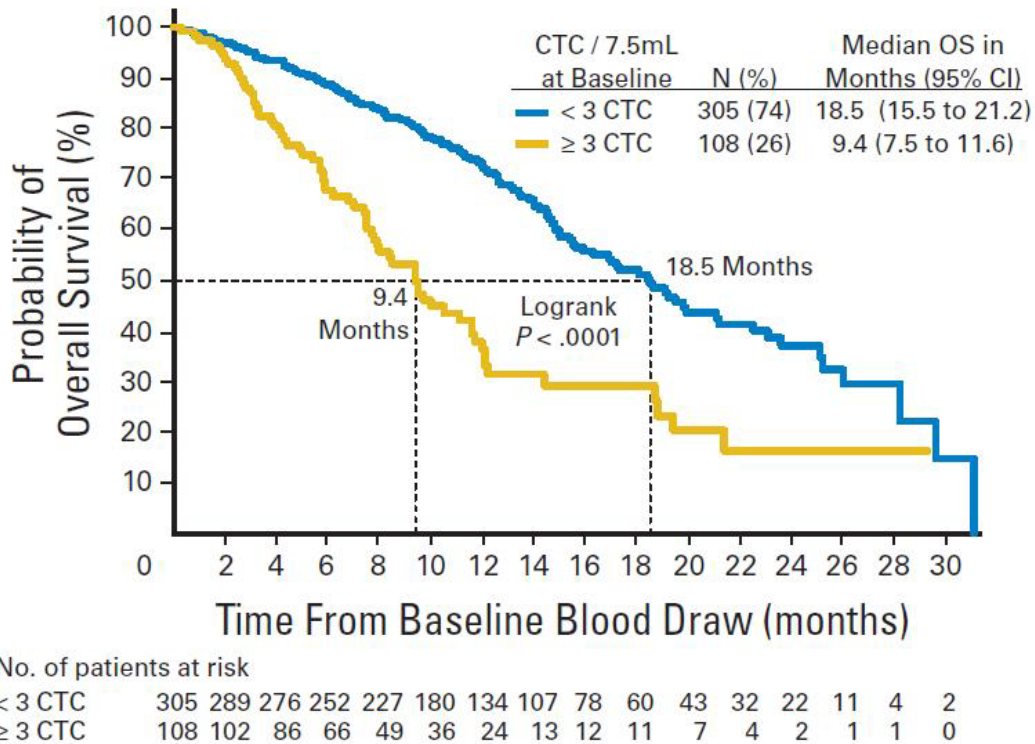


Figure 2 Probability of overall survival for favourable (<3 CTCs) and unfavourable (≥3 CTCs) patient groups (Cohen et al 2008).

Overall survival was also analysed for the four patient groups on the basis of CTC counts at baseline and three to five weeks. Results are summarised in Table 3.

Table 3 Median overall survival by CTC status at baseline and 3-5 weeks

| Group | CTCs/7.5mL at baseline | CTCs/7.5mL at 3-5 weeks | n (%) | OS, months [95% CI] |
|-------|------------------------|-------------------------|----------|---------------------|
| 1 | <3 CTCs | <3 CTCs | 227 (71) | 17.7 [14.7, 19.9] |
| 2 | ≥3 CTCs | <3 CTCs | 53 (17) | 11.0 [8.7, 18.1] |
| 3 | <3 CTCs | ≥3 CTCs | 9 (3) | 10.9 [0.6, NR] |
| 4 | ≥3 CTCs | ≥3 CTCs | 30 (9) | 3.7 [2.4, 8.4] |

OS = overall survival; NR = not reported

The analyses conducted by Cohen et al (2008), show that there is an association between peripheral CTC levels and progression-free and overall survival among metastatic colorectal cancer patients. Among these patients, those who had less than three CTCs per 7.5mL of blood showed significantly better prognosis. However, patients eligible for the study did undergo different lines of therapy (first, second or third line) and it is uncertain whether the variation in treatment regimes was *adequately* controlled for. Finally, this study was used to support FDA clearance of the CellSearch[®] system for enumeration of CTCs in metastatic cancer patients and the authors reported that the design was not intended to “assess whether a change in therapy based on unfavorable CTCs is beneficial” (Cohen et al 2008).

More recently, a prospective multicentre study in Japan investigated the relationship between CTC levels and response to therapy in patients with metastatic breast cancer using CellSearch[®] (Nakamura et al 2010) (level II prognostic evidence). Of the 118 patients, peripheral blood samples from 107 eligible patients were tested for CTCs before commencement of therapy (baseline), after their first cycle of therapy (3-4 weeks) and at 12 weeks. Levels of CTCs and radiographic findings were compared at baseline and 12 weeks. Hazard ratios were compared for patients with < 3 or ≥ 3 and for patients with < 5 or ≥ 5 CTCs.

Of the 118 enrolled patients, 76 (64.4%) had one or more CTCs, while 44 (37.3%) had five or more CTCs. Seven cases were observed to have a CTC count which decreased by more than 90 per cent from baseline after their first cycle of treatment, of whom six (85.7%) demonstrated either a complete or partial response to that treatment. Among the 11 patients whose CTC count increased from baseline after their first treatment cycle, seven (63.6%) had progressive disease. The hazard ratio for mortality among patients with ≥ 3 CTCs compared to those with < 3 CTCs was 2.26 (95% CI [1.10, 4.67]), *p*=0.027 and the hazard ratio for mortality among patients with ≥ 5 CTCs compared to those with < 5 CTCs was 3.07 (95% CI [1.50, 6.29]), *p*=0.002.

Another multicentre study enumerated CTCs in metastatic prostate cancer patients to determine their relationship to overall survival and possible prognostic application (de Bono et al 2008) (level II prognostic evidence). Patients (n=276) were categorised as unfavourable or favourable on the basis of < 5 or ≥ 5 CTCs per 7.5mL of peripheral blood, of whom 231 (84%) could be evaluated. The 132 (57%) patients with unfavourable pre-treatment CTC levels had an overall survival of 11.5 (95% CI [9.3, 13.7]) months compared to 21.7 (95% CI [21.3, NR⁵]) months for the favourable patient group with CTC levels of ≥ 5, *p*<0.0001. Unfavourable CTC counts at each of the four follow-up periods (2-5, 6-8, 9-12 and 13-20 weeks) also predicted shorter overall survival (*p*<0.0001). Finally, overall survival for patients with unfavourable baseline CTC levels who converted to favourable levels improved from 6.8 (95% CI [5.8, 10.3]) to 21.3 (95% CI [18.4, NR]) months, while overall survival for those who converted from favourable to unfavourable levels worsened from more than 26 (95% CI [21.4, NR]) to 9.3 (95% CI [8.2, 11.3]) months, *p*<0.0001.

The studies by Nakamura et al (2010) and de Bono et al (2008) drew similar conclusions to Cohen et al (2008), but without studies that directly address whether treatment modifications result in improved survival outcomes, the prognostic value of enumerating CTCs using the CellSearch[®] system is uncertain.

⁵ Not reached

COST IMPACT

A request was made to Veridex LLC to provide contact with a company representative, but no response was received before the date required by HealthPACT for consideration of the CellSearch[®] system.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

A portable filter-based micro-device for the detection and characterisation of CTCs has recently been developed (Lin et al 2010). The device differentiates between larger epithelial CTCs and smaller blood forming cells, and employs a membrane for CTC capture. It has been proposed for rapid processing in the office or at the bedside, thus negating the need for transportation to a central processing facility.

Recently, a study compared CTC detection using CellSearch[®] with the AdnaTest and reverse transcription PCR, however no survival nor other clinically relevant outcomes were assessed and therefore this study was not considered for inclusion (Van der Auwera et al 2010).

SUMMARY OF FINDINGS

The included studies provide evidence that CellSearch[®] contributes potentially useful prognostic information for metastatic colorectal, breast and prostate cancer patients. However, what these results mean in terms of changes to patient management remains unclear. The study by Cohen et al (2008) was used to support FDA clearance of the CellSearch system for enumeration of CTCs in metastatic cancer patients and was not designed to determine whether therapeutic changes based on unfavourable CTC count confers any advantage. Similarly, de Bono et al (2008) reported that their data led to FDA clearance of CellSearch[®] for CTC enumeration in metastatic prostate cancer patients. Nakamura et al (2010) did not disclose any such information, but their design was similar. Radiological techniques, used in all three studies, provide physicians with a means of assessing progression by the gross morphology of cancers, and are not amenable to direct comparison of prognosis as predicted by CTC levels. Consequently, CTC enumeration with CellSearch[®] could be better viewed as a potential adjunct to radiographic imaging. Stronger evidence of the prognostic value of CTC enumeration will depend on further comparative studies, preferably RCTs, that address whether changes to cancer therapy based on CTC levels early in the course of treatment provide improved progression-free and overall survival.

HEALTHPACT ASSESSMENT:

The available evidence was inconclusive of benefit from changes to cancer therapy based on CTC count and the unknown cost impact may create significant barriers to

uptake within mainstream practice. Therefore HealthPACT does not intend to further review this technology at this time.

NUMBER OF INCLUDED STUDIES

| | |
|-------------------------|---|
| Total number of studies | 3 |
| Level II evidence | 3 |

REFERENCES:

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SEARCH CRITERIA TO BE USED:

Circulating tumor* cells, CTCs
CellSearch, blood, cancer