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Nab-paclitaxel in combination with Gemcitabine for resected pancreatic ductal adenocarcinoma - Adjuvant Therapy

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LAY SUMMARY

Pancreatic cancer is cancer that starts in the pancreas, a gland that produces digestive juices and hormones. Pancreatic ductal adenocarcinoma where the cancer starts in the cells lining the ducts of the pancreas is the most common type of pancreatic cancer. Around half of all new cases are diagnosed in people aged 75 years or over. Pancreatic cancer rarely causes any symptoms in the early stages, so is often not detected until the cancer is fairly advanced. Surgery is the only curative treatment for patients with the early stage of the disease. Where surgery is not possible, treatment is aimed at prolonging survival, reducing symptoms and control the growth and spread of the tumour.

Paclitaxel formulated as albumin bound nanoparticles (Nab-paclitaxel) in combination with gemcitabine is being developed as a treatment option for patients with pancreatic cancer who have undergone surgery to increase the chances of being cured ('adjuvant therapy'). Both drugs are chemotherapies already being used to treat metastatic pancreatic cancer and other types of cancers and are administered by injection. If approved, the combination of Nab-paclitaxel and gemcitabine may increase the length of time that patients survive without any signs or symptoms of the cancer after surgery.

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TARGET GROUP

Pancreatic cancer (resected pancreatic ductal adenocarcinoma) – adjuvant therapy; in combination with Gemcitabine

TECHNOLOGY

DESCRIPTION

Paclitaxel formulated as albumin bound nanoparticles, (Nab-paclitaxel; Abraxane™; ABI-007) is designed to overcome the insolubility problems associated with conventional paclitaxel formulations. Paclitaxel is an anti-microtubule agent (a type of drug that blocks cell growth by stopping mitosis (cell division)) that promotes the assembly of microtubules (cellular structures that help move chromosomes during mitosis resulting from the assembly of α- and β-tubulin-dimers) from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.[1] This results in reduced ability of the affected cells to divide and grow.

Nab-paclitaxel in combination with gemcitabine is intended, and currently being trialled, as an adjuvant therapy for adult patients with resected pancreatic cancer. In the phase III clinical trial (the Apact study - NCT01964430), patients in the experimental arm were administered Nab-paclitaxel 125 mg/m^2 on Days 1, 8, and 15 of a 28 day cycle by intravenous (IV) administration, followed by gemcitabine 1000 mg/m2 on Days 1, 8, and 15 of a 28 days cycle by IV administration for a total of 6 cycles.[2]

Nab-paclitaxel in combination with gemcitabine is already licenced in the EU/UK for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Nab-paclitaxel in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Nab-paclitaxel is also indicated as a monotherapy for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.[1]

Nab-paclitaxel in combination with gemcitabine have been associated with a range of very common (≥1/10) and common (≥1/100 to <1/10) adverse reactions which are detailed in the in the summary of product characteristics (SPC).[1] The most common and important incidences of these adverse reactions include blood and lymphatic system disorders (anaemia, neutropenia, thrombocytopenia), peripheral neuropathy, sepsis and pneumonitis.[3, 4]

INNOVATION and/or ADVANTAGES

Nab-paclitaxel in combination with gemcitabine have previously demonstrated to have a synergistic effect when compared to monotherapy in increasing survival in patients with advanced/metastatic pancreatic cancer.[5] If licenced, this combination has the potential to increase disease free survival in patients with pancreatic cancer that have undergone surgical resection.

DEVELOPER

Celgene Ltd

AVAILABILITY, LAUNCH or MARKETING

Nab-paclitaxel in combination with Gemcitabine as an adjuvant therapy for resected pancreatic ductal adenocarcinoma is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Pancreatic cancer is cancer that starts in the pancreas, a gland that produces digestive juices and hormones. The most common type is adenocarcinoma associated with the exocrine gland, meaning that they start in cells that produce pancreatic digestive juices. More than eight out of 10 exocrine pancreatic cancers are adenocarcinomas. Nearly all of these are ductal adenocarcinomas. They start in the cells lining the ducts of the pancreas.[6]

Pancreatic cancer is more common in older people. Almost half of all new cases are diagnosed in people aged 75 years and over. Pancreatic cancer is uncommon in people under 40 years old. 1 in 71 people will be diagnosed with pancreatic cancer during their lifetime. It occurs equally in men and women. In the past 10 years, pancreatic cancer rates have increased and it is thought they will continue to increase. In England, pancreatic cancer is more common in people living in poorer areas. It is also more common in White and Black people than in Asian people.[6]

The pancreas is found deep within the body, leading to the inability to detect pancreatic cancer early-on. Most cases of pancreatic cancer go undetected due to the lack of obvious symptoms meaning the cancer often spreads to other organs. Risk factors associated with pancreatic cancer include smoking, diabetes, obesity, and a family history of pancreatic cancer.[7]

Patients are usually diagnosed with pancreatic cancer once they seek medical attention due to prolonged aggravated symptoms. This directly correlates with the vast majority of patients diagnosed within the latter stages of the disease. As the tumour grows larger and presses on nearby structures, the symptoms of pancreatic cancer become apparent. The types of symptoms experienced by patients largely depend on the location of the tumour within the pancreas. Tumours located at the head of the pancreas are associated with symptoms such as dark urine, pale-coloured stools, itching, vomiting, and nausea. In contrast, tumours located on the body or at the tail of the pancreas are associated with abdominal or back pain.[7]

Although knowledge of the underlying mechanisms of pancreatic cancer has advanced greatly over the last few years, surgical resection remains the only curative method. Patients who are classed as resectable (no regional or distant organ metastasis) are often treated by surgical intervention, depending on the location of the tumour within the pancreas. A laparotomy or surgical laparoscopy remains the only specific way to determine the resectability of the tumour, and can also confirm the staging of a tumour that is observed in a CT scan.[7]

The prognosis for pancreatic cancer is poor, and is largely dependent on the stage of the tumour at diagnosis. Patients with early-stage, localized, resectable tumours have the best prognosis and have a five-year survival rate of 24%. However, this group accounts for less than 20% of the pancreatic cancer population. In contrast, the five-year survival rate for patients with distant metastases is only 2%, with this segment making up approximately half the entire pancreatic cancer population.[8]

CLINICAL NEED and BURDEN OF DISEASE

Pancreatic cancer is the 11th most common cancer in the UK, accounting for around 3% of all new cases. In 2014, there were 9,618 new cases of pancreatic cancer in the UK, that is, 26 cases diagnosed every day. Incidence rates for pancreatic cancer are projected to rise by 6% in the UK between 2014 and 2035, to 21 cases per 100,000 people by 2035. This increase is due to a rapidly growing ageing population with incidence rates for pancreatic cancer in the UK highest in people aged 85 years and above.[9]

Pancreatic cancer is one of the most fatal cancers around the world, with the highest mortality rates found in developed countries. The high mortality rate is due to late diagnosis (up to 95% are diagnosed at an advanced stage), early metastasis and poor response to chemo- and radiotherapy.[7] There were around 8,800 pancreatic cancer deaths (ICD-10 C25) in the UK in 2014, it is the fifth most common cause of cancer death, accounting for 5% of all cancer deaths.[9]

Without treatment, the median overall survival for metastatic pancreatic cancer is approximately 12 weeks; this improves to approximately 6 months with treatment. In England and Wales, only 3% of people diagnosed with pancreatic cancer will survive their disease for five years or more. The Five-year relative survival for pancreatic cancer in men is below the European average in England, Wales, Scotland and Northern Ireland.[9]

In the 2016-17 period, there were 28,204 hospital admissions in England due to pancreatic cancer (ICD-10 C25), accounting for 35,813 finished consultant episodes (FCE) and 91,409 FCE bed days.[10] The total disability-adjusted life year (DALYs) and years of life lost (YLLs) due to pancreatic cancer in the UK were 112,884 years and 110,268 years, respectively.[11]

The population likely to be eligible to receive Nab-paclitaxel and gemcitabine as an adjuvant therapy for resected pancreatic cancer is estimated to be around 962 per year. This was estimated from the available pancreatic cancer statistics where 10% of patients diagnosed with pancreatic cancer (9,618 new cases in 2014) have surgery to remove the tumour as part of their primary cancer treatment.[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [TA476]. September 2017
- NICE technology appraisal. Guidance on the use of gemcitabine for the treatment of pancreatic cancer [TA25]. May 2001
- NICE clinical guideline in development. Pancreatic cancer: diagnosis and management in adults. [GID-CGWAVE0802]. Expected January 2018
- NICE guideline. Suspected cancer: recognition and referral. [NG12] June 2015
- NICE quality standard. Suspected cancer. [QS124]. June 2016
- NICE interventional procedure guidance. Laparoscopic distal pancreatectomy [IPG204]. January 2007

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO) Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[12]
- European Society for Medical Oncology and European Society of Digestive Oncology. Pancreatic adenocarcinoma: ESMO-ESDO clinical practice. Guidelines for diagnosis, treatment and follow-up. 2012.[13]

CURRENT TREATMENT OPTIONS

Following staging of the tumour, pancreatic cancer can be categorised as resectable, borderline resectable, locally advanced or metastatic disease. A treatment decision must be taken in accordance with these findings, including general and nutritional status considerations.[12] The only curative treatment of pancreatic cancer is radical surgery. This approach is mainly suitable for patients with early stage of disease mainly stage I and some stage II, where the tumour involves the pancreas and surrounding structures, such as the small bowel, bile duct or stomach but has not affected any of the nearby major blood vessels.[13, 14]

Considering the poor results of surgery alone in pancreatic carcinoma, many efforts involving chemotherapy, radiotherapy or both have been made to improve the 5-year survival of these patients.[12] Postoperatively, 6 months of chemotherapy with gemcitabine or 5-fluorouracil (5-FU) chemotherapy are recommended.[13] Other types of adjuvant therapy may include gemcitabine in combination with capecitabine and FOLFIRINOX (5-FU, oxaliplatin and irinotecan).[14] The role of adjuvant chemoradiation is controversial and the recommendation is that no chemoradiation should be given to patients after surgery except in clinical trials.[12]

If the tumour is deemed not resectable, the aim of treatment is prolongation of survival and palliation of symptoms related to the disease by optimal local control and control of metastatic growth.[12, 13]

EFFICACY and SAFETY

Trial	**The "Apact" Study, NCT01964430; Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone; phase III**
Sponsor	Celgene
Status	Ongoing, not recruiting
Source of Information	Trial registry[2], Celgene Ltd.
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, active-controlled, open-label, parallel assignment
Participants	n=866; aged ≥18 years; histologically confirmed resected ductal pancreatic adenocarcinoma with macroscopic complete resection; pancreatic cancer surgical staging: T 1-3, N0-1, M0; should be able to start treatment no later than 12 weeks post-surgery.
Schedule	Randomised to nab-Paclitaxel 125 mg/m2 on Days 1, 8, and 15 of a 28 day cycle by intravenous (IV) administration, followed by gemcitabine 1000 mg/m2 on Days 1, 8, and 15 of a 28 days cycle by IV administration for a total of 6 cycles; or Gemcitabine 1000 mg/m2 on Days 1, 8, and 15 of a 28 day cycle by IV administration for a total of 6 cycles

Follow-up	Follow-up occurred from time from the date of randomization to the date of disease recurrence or death, whichever is earlier.
Primary Outcomes	Disease Free Survival (DFS) [Time Frame: up to approximately 9 months] Time from the date of randomization to the date of disease recurrence or death, whichever is earlier. (Disease recurrence will be determined by independent radiological review of computed tomography (CT) or magnetic resonance imaging (MRI) scans.)
Secondary Outcomes	Overall Survival [Time Frame: up to approximately 18 months]; Time from the date of randomization to the date of death Number of Participants with Adverse Events [Time Frame: up to approximately 18 months] Assessment based on AEs, SAEs, laboratory abnormalities.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated Study Completion Date is reported as 1 October 2020.

ESTIMATED COST and IMPACT

COST

Nab-paclitaxel in combination with gemcitabine is already marketed for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. NHS indicative price of Nab-paclitaxel (Abraxane™) 100mg powder for suspension for infusion is £246.00 per vial (Hospital only).[15] Treatment with 125mg/m^2 on days 1, 8 and 15 of a 28 day cycle would cost £2,214.[a]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Increased length of survival

☒ Reduced symptoms or disability

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services: *short increase in drug delivery time (30 minutes) as Abraxane is administered before gemcitabine.*

☐ Decreased use of existing services

[a] Based on average surface area of 1.88m^2.

☐ Re-organisation of existing services

☐ Need for new services

☒ Other: *possible increase in hospital admissions due to additional toxicities e.g. febrile neutropenia as a result of myelosuppression.*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs: *specify*

☐ Other reduction in costs: *specify*

☐ Other: *specify*

☐ None identified

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