

TPS265[^] Docetaxel, cisplatin (TP), and radiation with or without cetuximab in advanced larynx carcinoma (DeLOS II trial)

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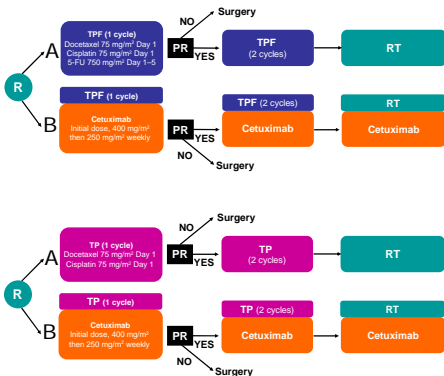
Abstract

Background: The DeLOS II trial is a German multicenter (25 centers) randomized phase II trial investigating a docetaxel/cisplatin/5-fluorouracil (TPF) induction chemotherapy with or without cetuximab for patients with only by laryngectomy operable carcinoma of the larynx/hypopharynx, followed by radiotherapy. The goal is to preserve a functional larynx.

Methods: Arm A: standard TPF (TP since Aug 2009). Radiation start in week 11; Arm B: Same treatment as arm A with the addition of cetuximab day 1 400 mg/m² i.v. followed by weekly 250 mg/m² i.v. for 16 weeks. Patients with no response after 4 weeks (first cycle) receive laryngectomy. Planned accrual is 85 patients per treatment arm (170 total).

Primary Outcome Measures: Confirmatory proof of an adequate survival rate with a functionally larynx-conserving 2 years after randomization.

Current follow up: Total enrollment in January 2010 was 78 patients. Due to four toxic deaths among the first 62 treated patients (3 in arm A and 1 in arm B), 5-FU was omitted from the induction chemotherapy, and accrual continues with TP with or without cetuximab + radiation due to 4 TPF-related toxic deaths. TPF with or without cetuximab is an effective, albeit toxic induction chemotherapy regimen for patients with SCC of the larynx. SCC of the larynx is often associated with a history of excessive smoking and the expected comorbidities, which may explain the degree of toxicity, which is unacceptable for operable carcinoma patients. TP with or without cetuximab may be an alternative for patients, to whom induction-chemotherapy followed by radiation is indicated for larynx preservation.



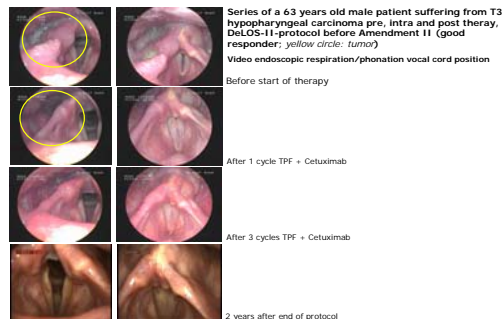
Start of the DeLOS-II trial July 2007

Stop February 2009 due to 4 toxic deaths (3 in arm A and 1 in arm B) after 62 patients

Start again after Amendment II in August 2009. Skip of 5FU

26.05.2010: 90 patients treated

ClinicalTrials.gov Identifier: NCT00508664



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SAE-Reporting April 2009 for decision making Amendment II (red: deaths)

Body System (ADR Term)	Treatment Arm A (cases)	Treatment Arm B (cases)	Treatment Arm A (individual patients)	Treatment Arm B (individual patients)
Blood and lymphatic system disorders				
Neutropenia	12	17	8, 16, 22, 30, 30, 30, 31, 33, 34, 34, 45, 77, 77, 83, 84, 91	4, 4, 18, 26, 27, 27, 31, 31, 33, 34, 34, 45, 77, 77, 83, 84, 91
Leukopenia	12	14	22, 30, 30, 30, 30, 44, 44, 46, 47, 79, 85, 89	17, 18, 28, 31, 31, 31, 33, 34, 34, 35, 77, 83, 84, 91
Gastrointestinal disorders				
Mucositis oral	0	1		5
Abdominal pain	0	1		17
Stomatitis	1	0	22	
Diarrhea	1	0	96	
Diarrhea fatal	1	0	89	
Colitis ischaemic	1	0	96	
Fatal enteritis	1	0	96	
Gastrointestinal necrosis	1	0	96	
Cardiac disorders				
Decompensated heart failure	1	0	32	
Tachyarrhythmia absoluta	1	0	32	
Infections and infestations				
Sepsis	1	0	96	
catheter related infection	0	1		5
Clostridium perfringens infection fatal	1	0	13	
Neutropenic infection	1	0	32	
Staphylococcus epidermidis infection	0	1		18
Clostridium difficile colitis fatal	0	1		38
General disorders and administration site conditions				
Reduced general condition	4	2	8, 47, 85, 85	27, 84
Multorgan failure, fatal	1	0	96	
Fever	1	0	32	
Mucositis	0	2		17, 38
Renal and urinary disorders				
Kidney failure fatal	1	0	89	
Renal failure acute	0	1		18
Flushing	1	0	96	

Primary Outcome Measures:

Confirmatory proof of an adequate survival rate with a functionally larynx-conserving 2 years after randomisation (time frame: LFS-rate 2 years after randomisation)

Secondary Outcome Measures:

Descriptive analysis of the study arms concerning the secondary end criteria of the study (time frame: LSF 2 years after randomisation)

Explorative comparison of the study arms concerning the primary and secondary end criteria of the study (time frame: LSF 2 years after randomisation)

- Estimated enrollment: 170
- Study start date: July 2007
- Estimated primary completion date: July 2013 (Final data collection date for primary outcome measure)

Inclusion Criteria: Ages Eligible for Study: 18 Years to 75 Years
Genders Eligible for Study: Both

- Histologically confirmed, primary only with laryngectomy resectable squamous-cell carcinoma of the larynx or hypopharynx
- T2-T4a carcinoma of the glottis
- T2-T4a carcinoma of the supraglottic, only controllable by laryngectomy and if applicable by resection of longitudinal muscles
- T2-T4a carcinoma of the hypopharynx only controllable by laryngectomy (for example T2, post- or long- and hypopharynx segmental resection)
- No distant cervical metastases (NO-N2) have to be resectable by surgical procedures
- Blood Chem: Leukocytes > 3000/mm³; Neutrophils > 1000/mm³; Thrombocytes > 80000/mm³
- Clinical chemistry
- adequate renal function, defined by serum creatinine and area not higher than 25% upper NL, creatinine-clearance > 60 ml/min/1.72 m²
- adequate hepatic function with SGOT, SGPT not higher than 50% and bilirubin not higher than upper NL
- electrolytes at NL
- anaesthetic risk normal or low-grade elevated
- written informed consent
- effective contraception after individual advice for men and women if there is a possibility of reproductive potential (effective contraception are: oral contraception with estrogen and gestagen (20 mg/0.1), vaginal ring, intrauterine device, minipill, hormone free, implantation, hormonal releasing implantation (local hormone containing not), abstinence or vasectomy (sterilization) of the male)

Amendment 1 (01.08.2008 PEI)

Before start of TPF prophylactic antibiotic treatment (Clindamycin) is mandatory. Strong introduction to the patients that immediate presentation at the hospital if fever >38°C occurs after demission. If enteritis clostridium difficile testing should be performed to exclude candidates for septic deaths.

Amendment 2 (08.07.2009 PEI)

Due to four toxic deaths among the first 62 patients (3 in arm A and 1 in arm B), 5FU was omitted from the induction chemotherapy, and accrual continues with TP with or without cetuximab + radiation. The decision of the data safety board was based on the well known 5FU toxicity causing vesicle damage. Even in head and neck cancer patients with tobacco related high vesicle morbidity additional damage of vesicles could be responsible for fatal conditions.

Amendment 3 (immediate change effective since 18.09.2009; amendment 3 05.2010 PEI)

Prophylactic Clindamycin was substituted by Levofloxacin. In case of resection disorders hospitalisation while induction chemotherapy is mandatory.

