MINUTES OF THE ANTIFOLATE ADVISORY PANEL MEETING, OCTOBER 28TH AND 29TH 1997, WASHINGTON DC.

Present:

Panel:
Dr. Dan Von Hoff (Chair)
Prof. Hilary Calvert
Prof. Herbie Newell
Dr. Luis Paz Ares
Prof. Hans Schmoll
Dr. Carmen Allegra
Dr. Peter Dannenberg
Prof. Jean Louis Missett
Dr. Robert Allen

LY 309887 Investigators (afternoon 29th October)
Dr. Eric Rowinsky
Dr. Cheryl Aylesworth
Dr. Sharyn Baker
Prof. Herbie Newell
Prof. Hilary Calvert

Lilly:
Diana Kelley
Mark Miller
Don Thornton
Jerry Thompson
Steve Hamburger
Jackie Walling
Victor Chen
Rick Schultz
Barbara Sterner

Agenda
As previously published except item 7 (MTA investigator meeting discussion), which was deferred.

MINUTES

COLORECTAL CANCER.

MTA data. Front-line RR% = 17%. Survival 14.5 months. Secondline: as yet no responses, TTP is 1.6 months. This compares with historical data for CPT 11 in this setting of 2.6 months. However, details of patients prior 5 FU therapy was not available. Third line: no responses, TTP = 2.3 months.

Future development: Third line: Probably should give up. Only possible future study would be randomized against BSC.

Secondline. We need to understand prognostic factors of the patient population exposed and to check the TTP figures. If one were to proceed the study that would be needed would be a randomized study vs. CPT 11. However emerging data suggests that CPT11 would be very hard to beat in this setting. The response rates in 3 studies of CPT 11 were: 21, 17 and 12.5%, with the latter two studies being conducted by community oncologists

Front-line. We need to decide whether a study of monotherapy MTA is needed to demonstrate the value of MTA, or whether one should only proceed in combination. As monotherapy, one would need to randomize against either 5FU or Tomudex. One would need to demonstrate either better survival or equivalent survival with better QOL. It would be preferable to randomize against the Mayo clinic schedule of 5 FU since this is more tox and less efficacious than the continuos infusion or DeGramont regimes, or at least is perceived to be so. Alternatively it might be possible to randomize against the physicians choice of 5 FU regime. There was some divergent opinions about the need to do this study. Some members thought that it was the only possibility of demonstrating a survival benefit. Prof. Missett and Prof. Schmoll thought that the study should be done. Dr. Paz Ares and Prof. Missett thought that Tomudex was a useful drug. In particular the Q3 week schedule is attractive.

In combination, the issue here is the large number of new players. This is an issue not only from a regulatory hurdle perspective, but also in terms of competition for clinical trial patients. For example the combination of 5FU and oxaliplatin is reported to have a response rate of 50%, with median duration of survival of 17 to 18 months. There is also an ongoing study of 5FU and CPT 11 in front-line therapy and a study of CPT11 and 5FU is in the planning stages. One possible study design for a randomized trial (dependent obviously on phase I data being permissive) would be MTA CPT11 vs. 5FU CPT11. Although it has proven difficult to combine MTA with 5 FU, the panel felt that it was important to persevere with this combination, even if a low dose of 5FU had to be taken into phase II clinical trial.

NB Buyse has published a useful overview showing that both TTP and RR% are poor predictors of eventual survival in colorectal cancer.

Daily x 5.
The panel felt that this schedule should only be examined further in other tumors if the colorectal data were positive (currently too early). Daily x 5 topotecan is not acceptable in the palliative setting in France, because of the QOL factor.

NSCLC
MTA Data: there is a 20 to 25 % response rate in two multicentric phase II studies, one of which is complete (Canadian) and the other ongoing (South Africa and Australia) . The responses from the Canadian study have been independently validated.
Although a number of responses were seen in stage IIIb disease, there was a 17% RR in stage IV disease.

Conclusions
1. Need greater confidence in the phase II setting (i.e. more data)
2. In a phase II study of MTA plus cisplatin, one would be looking for a 1 yr. survival of 50 to 60%, with a response rate of 40%

JMBQ
This is a study in a secondline setting for patients with either stage IIIb or IV disease, who have failed 1 prior regime containing platinum and a taxane. The study is a phase II / III design. In the phase II portion patients will be randomized to MTA vs. Navelbine, and the primary endpoint of this study will be response rate. Assuming sufficient activity for MTA the study will continue to a phase III, where survival will be the primary endpoint. Additional endpoints will include TTP, response, clinical benefit ? QOL (to be decided), and safety. Patients will be stratified for response on prior therapy (yes or no), chemotherapy free interval , performance status, and baseline homocysteine levels (see later discussion for information in respect of functional folate status, and a modification to this design, based on the need to evaluate the effect of vitamin supplementation on toxicity).

Richard Schilsky liked this study design

Further development: Parallel path the development of MTA in NSCLC in second and front-line settings. The preferred route to registration would obviously be in a secondline setting (speed, fewer competing players). Even in a secondline setting, response rate is not viewed as a useful endpoint.
Taxotere was turned down on initial application to the FDA, which was based on response rate. RPR were told to do a randomized trial.

One possible study in a front-line setting would be MTA plus Carboplatin vs. Carboplatin Taxol. CALGB is currently doing a study of carboplatin Tax vs. Tax in patients with stage IV disease.

BREAST CANCER
MTA data: An approximate 30% RR in a single phase II study in patients of whom some had received prior chemotherapy for metastatic disease
Future development: If MTA has sufficient activity in patients that have failed anthracyclines and taxanes (JMBT phase II), then Rick Schilsy felt that a randomized study would be needed in the US. A phase II with an approximate 18 to 20 RR% will not suffice. However the caveat to that is that a number of phase II studies involving a large number of patients, ie at least 150, with a consistent RR% of 18 to 20% MIGHT however suffice. Capecitabine has a response rate of 20 to 23 % in this patient population with good TTP.

Potential study designs for a randomized study in these patients would include MTA plus Navelbine vs. Navelbine, 5 FU (this would also be a good study to differentiate MTA from a mechanistic point of view. Possible alternatives would included MTA vs. 5FU, MTA vs. Mitomycin C, or MTA vs. Navelbine. There is a study of 5FU and oxaliplatin just starting in this patient population (note: where is this study being done? In France?, and is this a phase II?). The combination of MTA plus oxaliplatin is possible in this setting, but obviously phase I data is needed.

NB. Dan Von Hoff bet Hilary Calvert that the response rate of MTA would not be more than 30% in this patient population. Hilary accepted the bet!

MTA might have a role in the adjuvant setting, when combined with an alkylating agent. In the second line setting after failure of anthracyclines, a randomized trial of MTA plus Taxotere vs. Taxotere would be appropriate.

The panel felt that an anthracycline combination was of lower priority than some of the other studies.

BLADDER CANCER
MTA phase II: This is a study in which patients have had no prior chemotherapy for metastatic disease. Currently 19/ 24 patients are evaluable. The response rate is approximately 27 %, and at least 2 of the patients have had decreases in tumor volume of at least 85%. There has been an excess of toxicity, particularly myelosuppression, and a number of patients have had reduced creatinine clearance. Action; look at creatinine Clearance criterion in the protocol, is it too high for repeat dosing, or should we be dose

reducing in the event of a Cr Clearance of say < 60...this would need to be determined from inspection of the data

Further development: This is difficult given the number of new agents being evaluated in bladder cancer, and the high response rates obtained (including gemcitabine)

ECOG are currently doing a study of gemcitabine vs. piritrexim

HEAD AND NECK CANCER
MTA Data: This is a 2nd line study conducted in France. Currently there are 4/7 partial responses in the study with a further patient reported to be "responding". No patients have yet had progressive disease. All patients have had 5FU and cisplatin front line. The chemotherapy free intervals in 3 of 4 of the responders are 8, 10 and 12 months respectively

Future studies: In patients that have failed 5FU and cisplatin front-line, a randomized study comparing MTA to methotrexate. This is identical to the study design used by Aguoron in evaluating Thymitaq, where the response rate is reported to be 13% for Thymitaq. This type of study could be difficult to do in the US, where patients typically would receive radiotherapy and Taxol in this setting. However it might be possible to do this study elsewhere, Pakistan is worth considering for example.

Another possible study design would therefore be to randomize against Taxol in a second line setting

As a prelude to moving into a front-line setting, it would be necessary to conduct a phase II study with MTA plus cisplatin. Another option in an adjuvant setting might be MTA plus XRT vs. XRT. However both preclinical and clinical data with this combination is required before this study could be done.

CERVIX.
MTA data. This is confounded by the loss of many (if not all) responders to follow up . Hence a replicate study is needed.

Future data: It may be necessary to use a cooperative group in order to get sufficient patients , GOG might be a possibility. Mexico would be a good source of cervix patients. In front-line, an appropriate phase III randomized trial would be MTA vs. cisplatin.

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